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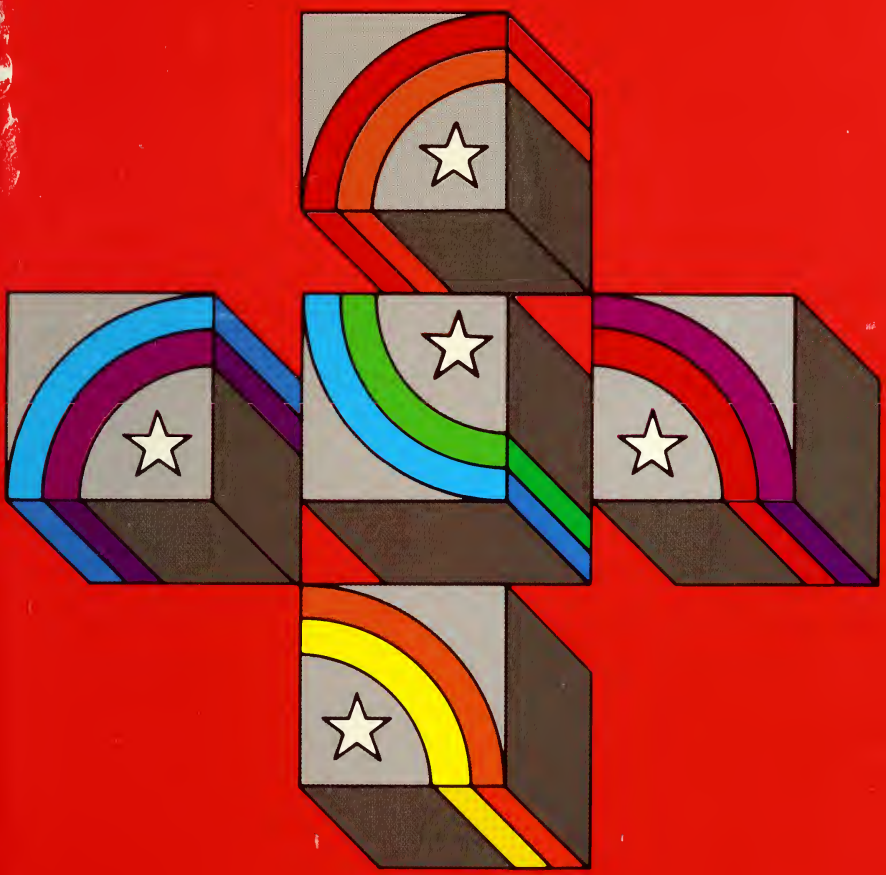
The Medical Staff Fellowship Program at the National Institutes of Health

1987 Catalog



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

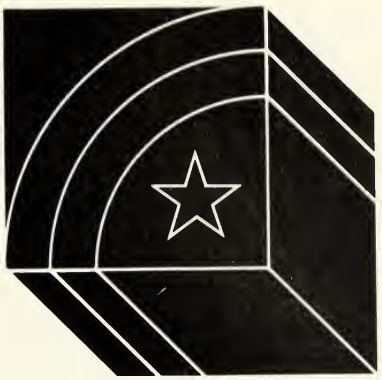
National Institutes of Health

Contents

Part Four
Academic Programs Available to Medical Staff Fellows

Part One

General Description of Medical Staff Fellowships and Other Opportunities



The Warren Grant Magnuson Clinical Center

John L. Decker, M.D.,
Director

The Warren Grant Magnuson Clinical Center is a modern laboratory hospital facility shared by the 11 Institutes that conduct combined laboratory and clinical study programs. This 540-bed research hospital is located on a 300-acre campus at the National Institutes of Health (NIH) in Bethesda, Maryland.

NIH is the largest biomedical research organization in the world. Approximately 2,600 staff members have doctoral degrees, including almost 1,000 with M.D. degrees, more than 1,500 with Ph.D. degrees, and about 40 with D.D.S. and 50 with D.V.M. degrees. A significant number have more than one doctorate.

Three Nobel laureates work on the campus: Drs. D. Carleton Gajdusek, Julius Axelrod, and Marshall W. Nirenberg. Dr. Gajdusek received the award in 1976 for his work in proving that kuru—a fatal disease affecting the nervous system—is a transmissible slow virus infection.

In 1970, Dr. Axelrod was cited for discoveries concerning transmitter substances in nerve terminals and mechanisms for their storage, release, and deactivation. Dr. Nirenberg was honored in 1968 for his work on the translation of the genetic code and its function in protein synthesis.

Three other scientists received the Nobel prize for work done while at NIH. In 1976, Dr. Baruch Blumberg was honored for his discovery of the "Australia antigen," a marker of hepatitis B. The prize was given to Dr. Christian Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA.

With the help of a staff of almost 3,000 technical personnel, NIH scientists are involved in some 2,500 research projects which result in more than 5,000 published scientific articles each year. The budget for this intramural research effort is approximately $486 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physi-

cians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care.

The Nuclear Medicine Department provides whole-body scanning and diagnostic imaging through the use of radioactive pharmaceuticals. Positron emission tomography and radionuclide cineangiography are among the imaging techniques under study. The superbly equipped clinical pathology laboratories provide optimum support to physicians and their patients. The Department of Transfusion Medicine provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for medical staff fellows to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of staff fellows in the use of computers in medicine.

A large, computer-based Medical Information System is used in support of patient care in the Clinical Center and the adjoining Ambulatory Care Research Facility. Two hundred display terminals and 85 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patient care process is available through the central NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 8,700 patients yearly. In addition, the outpatient clinics service over 147,000 patient visits annually.

A newly completed 13-story Ambulatory Care Research Facility (ACRF), adjacent to the original Clinical Center structure, is designed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center. The facility will provide an optimum environment to care for and study outpatients, yet it will retain the same proximity between clinical and laboratory scientists that has successfully promoted medical inquiry in the existing Clinical Center.

The Clinical Center appoints medical staff fellows for the departments of Clinical Pathology, Critical Care Medicine, Nuclear Medicine, and Transfusion Medicine. These programs are described in part three.

The Medical Staff Fellowship Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as medical staff fellows at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Medical Staff Fellowship Program (formerly the Associate Training Program and encompassing what used to be designated clinical, research, and staff associate positions) are based on professional attainment, research interest, and ability. The NIH seeks outstanding candidates and selection is made without regard to race, sex, geographical location, or university affiliation. Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process explained in part two.

Each medical staff fellow participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each staff fellow's experience. Because of the unique blend of clinical and nonclinical scientists, the staff fellow is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorials to sponsored lectureships. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc., is available on a broad range of topics, including mathematics, languages, laboratory skills, and clinical reviews (see part four).

The NIH affords the medical staff fellow the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

Some fellows devote most of their time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the staff fellow to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The medical staff fellow position also provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical categories. In these cases, the staff fellow may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he or she works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

The Dental Staff Fellow

Like medical staff fellows, the dental staff fellow may participate in laboratory and clinical research, and enhance professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the fellowship, there is full opportunity for a fellow to become familiar with all ongoing research programs relevant to dentistry; affiliate with one or more preceptors to participate in a mutually acceptable area of investigation; and extend scientific background through rounds, conferences, seminars, and formalized course work.

The Medical Staff Fellow in Pharmacology (Pharmacology Research Associate Program)
Staff fellows in this program, sponsored by the National Institute of General Medical Sciences, spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

Staff Physicians
Some physicians, already qualified in a specialty, are not appointed as medical staff fellows but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to medical students. For 1986-87, the staffs of several Institutes are collaborating to supply an in-depth exposure to 15 clinical subspecialties: anesthesiology, clinical dental care, critical care medicine, computers in clinical medicine, endocrinology and metabolism, genetics, geriatrics, immunology, medical-surgical neurology, neurobiology, nuclear medicine, oncology-hematology, psychopharmacology, pediatric psychopharmacology, and surgical oncology.

The essence of this educational experience is close association between the student, staff fellows, and physician-scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Clinical Electives Program Office
Building 10, Room 2N226
National Institutes of Health
Bethesda, MD 20892

Approved Training Programs

Residency training programs approved by the Accrediting Council on Graduate Medical Education are offered in anatomical pathology, nuclear medicine, allergy and immunology, and transfusion medicine as are fellowships for advanced subspecialty training in transfusion medicine, and clinical pathology, including clinical chemistry, hematology, and microbiology, and the laboratory computer service.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Anatomical Pathology
Lance A. Liotta, M.D., Ph.D.
Chief, Laboratory of Pathology
Building 10, Room 2A33
National Institutes of Health
Bethesda, MD 20892

Nuclear Medicine
Steven M. Larson, M.D.
Chief
Nuclear Medicine Department
Building 10, Room 1C401
National Institutes of Health
Bethesda, MD 20892

Allergy and Immunology
Michael M. Frank, M.D.
Clinical Director
National Institute of Allergy and Infectious Diseases
Building 10, Room 11N228
National Institutes of Health
Bethesda, MD 20892

Transfusion Medicine
Harvey G. Klein, M.D.
Chief
Department of Transfusion Medicine
Building 10, Room 1E33
National Institutes of Health
Bethesda, MD 20892

Board Certification: The first year of the clinical fellowship in the National Heart, Lung, and Blood Institute is accredited as a third year of training in internal medicine by the American Board of Internal Medicine.

The first year of the clinical fellowship in the National Institute of Mental Health is accredited as the final (PG-4) year of training in psychiatry.

The 3-year medical staff fellowship has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Credit towards board certification is offered in the following specialties and subspecialties:

Allergy
Clinical chemistry
Critical care medicine
Dermatology
Endocrinology
Hematology
Gastroenterology
Infectious diseases
Internal medicine (NHLBI only)
Medical genetics
Medical oncology
Microbiology
Neurology
Pediatric endocrinology
Pediatric genetics
Pediatric hematology/oncology
Pediatrics
Psychiatry
Reproductive endocrinology
(obstetrics and gynecology)
Rheumatology
Transfusion medicine

The amount of credit earned depends on the training completed and the acceptability of such to the individual board. Candidates are advised to consult the appropriate Institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During this clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 540-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Medical staff fellows selected by any of the three endocrinology branches of

the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) as well as the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Medical staff fellows from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Lectures and Courses
The NIH campus provides a stimulating intellectual environment for continuing education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. The endocrinology fellowship program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an intensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program
Students selected from various medical schools throughout the country participate in endocrinology courses offered three times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations
Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the fellowship program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Bruce D. Weintraub, M.D., Building 10, Room 8N315, National Institutes of Health, Bethesda, MD 20892.

Medical Genetics Program

The NIH Interinstitute Medical Genetics Fellowship Program is a cooperative undertaking involving several clinical branches and research laboratories in various Institutes located on the Bethesda campus. It is a program of 2-, or in rare cases, 3-year duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is also designed to fulfill all requirements proposed by the American Board of Medical Genetics for fellowships leading to eligibility for Board certification. Accreditation of the Program by the Board is awaiting Board action and is anticipated.

The fellowship includes clinical activities and laboratory or clinical investigations under the direction of a senior scientist. Fellows are responsible for outpatients seen at the weekly NIH Genetics Clinic. They also serve as genetics consultants in the 540-bed Clinical Center and participate in weekly patient conferences and ward rounds. Further opportunities to become familiar with the spectrum of patients with genetic disease are provided by attendance at genetics clinics at collaborating institutions including the Johns Hopkins Hospital, Children's Hospital National Medical Center Pediatrics Genetics Unit, George Washington University Wilson Unit (Prenatal Diagnosis), and the Genetics and IVF Institute.

Entrance into the Medical Genetics Program is through either of two routes: 1) fellows may apply to it directly, be in-

terviewed by representatives of the Program's Steering Committee, and at the same time or after being accepted by the Program, choose a laboratory in which to do research; alternatively, 2) fellows may apply to a research branch or laboratory in one of the participating Institutes, be interviewed by the representatives of that Institute, and then, after being accepted by that Institute and arriving at NIH, apply for entrance into the Medical Genetics Program. (Each research unit may have clinical requirements in addition to those of the Medical Genetics Program). Candidates choosing the second route will be interviewed after they have begun their NIH Fellowships by the Program's Steering Committee which will decide their acceptability.

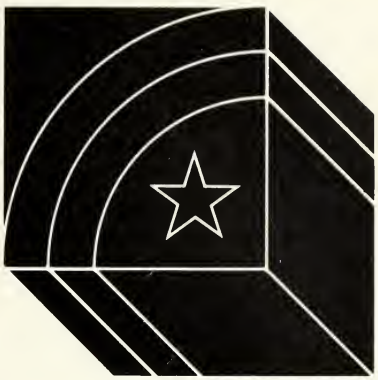
Fellows in the Medical Genetics Program pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating scientists are provided in a brochure which will be supplied to fellowship applicants. The aim of this program is to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in medical genetics.

The fellowship program includes a seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, a year-long didactic course in clinical aspects of genetics (mandatory for first year fellows), and a journal club. Other opportunities for continuing education (clinical and basic science conferences, tutorial seminars, and postgraduate courses) are plentiful on the NIH campus and are encouraged. The fellowship program also sponsors a yearly 8-week elective in medical genetics for senior students from medical schools around the country; fellows assist in didactic lecture-demonstrations on the approach to patients with genetic diseases and in supervision of students in patient-related activities. These and other teaching opportunities develop the fellows' skills as educators in preparation for future academic careers.

Applications for the fellowship program should be directed to the Medical Staff Fellowship Office (see p. 9). Further information may be obtained by telephone from Drs. John J. Mulvihill or Dilys M. Parry at (301) 496-4947.

Part Two

Applying for a Medical Staff Fellowship



About 125 medical staff fellows are appointed annually to positions emphasizing clinical or basic research. Fellows are employed through the Public Health Service (PHS) in special civil service appointments, but not in the Commissioned Corps of the PHS.

Minimum eligibility requirements for most medical staff fellowships is completion of 2 years of graduate medical training before entrance on duty. Application should be made between 1 and 2 years before desired date of appointment.

To be considered for a medical staff fellowship, completed application forms must be received in the NIH Medical Staff Fellowship Office, Building 10, Room 2N226, National Institutes of Health, Bethesda, MD 20892, by November 14, 1986.

Participants in the National Health Service Corps Scholarship Program are not eligible for consideration until after they have served obligated pay-back years in NHSC-designated areas of medical need.

To be eligible for a PHS appointment as a medical staff fellow (not in the Commissioned Corps), a candidate must meet the following requirements:

- Be a United States citizen or a permanent U.S. resident.
- Meet the medical fitness standards.
- Be a graduate of an accredited medical, osteopathic, or dental school.
- Satisfactorily complete an internship (PG1) approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)
- Foreign medical graduates—foreign nationals or American citizens who have received their medical degree from a medical school outside the United States, Puerto Rico and Canada and that is listed in the World Health Organization's *World Directory of Medical Schools*—must be certified by the Educational Commission for Foreign Medical Graduates (ECFMG). ECFMG certification may presently be obtained by passing the ECFMG examination, Visa Qualifying Examination (VQE) or the Federal Licensing Examination (FLEX). In July 1984, a new two day Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS) replaced the ECFMG and VQE examinations.

Employment Benefits for Medical Staff Fellows

Medical staff fellows are entitled to the following benefits which are comparable to those offered to Civil Service employees: partial subsidy for health insurance and group life insurance, retirement benefits, occupational medical emergency service at NIH, compensation for injury, 13 working days of annual leave per year and the same amount of sick leave, and training at Government expense. Moving expenses (travel and transportation of household goods) up to a maximum of $2,500 will be provided to medical staff

fellows entering on duty. No return expenses will be provided.

Method of Selection—Matching Program

Selections for medical staff fellow appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

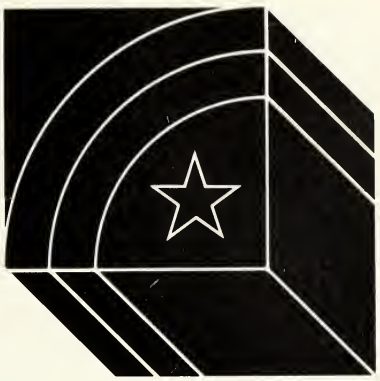
In the application packet, a candidate will find several sheets, each headed "Program Area Selection Checklist." After reading part three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested. There is no limit to the number of interest areas which may be checked. The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review by the Institutes of all applications, a limited number of candidates will be selected for personal interviews after which the candidate submits his or her confidential preference list. *Applicants should only list programs in which they have an interest and would accept if chosen. In a highly competitive selection system, failure to accept a position after the "match" compromises another candidate's opportunities.*

The NIH Medical Staff Fellowship Office will set up the interview and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

Part Three

Program Areas for Which Candidates May Apply



Each of the major NIH components has prepared a description of its program areas for which medical staff fellows may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *It should be noted that a candidate is not limited as to the number of kinds of positions for which he or she may apply.*

National Cancer Institute

Vincent T. DeVita, Jr., M.D.,
Director and Clinical Director

Division of Cancer Biology and Diagnosis

—Alan S. Rabson, M.D., Director

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states.

The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief. Medical staff fellow positions are available in many of these areas and fellows work exclusively with the branch or laboratory in which they are accepted. All fellows have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Appointments in Clinical Research

Clinical positions are available for medical staff fellows in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Fellows participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Appointments in Laboratory Research

Nonclinical positions are available in the following laboratories: Biochemistry, Molecular Biology, Immunobiology, Cell Biology, Genetics, Mathematical Biology, Tumor Immunology and Biology, and Cellular Oncology.

In general, fellows are engaged in original research under guidance of individual investigators who act as preceptors for the fellows.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NCI programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Clinical Research Branches

Dermatology Branch—
Stephen I. Katz, M.D., Ph.D.
Senior Investigators
- Thomas Lawley, M.D.
  Gary Peck, M.D.
  Jay Robbins, M.D.
  John Stanley, M.D.
  Peter Steinert, Ph.D.

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic, neoplastic, and inflammatory states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin, and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; physiology of lymphoreticular cells and lymphokine formation; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; genodermatoses; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; clinical, chemical, and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

Immunology Branch—
David H. Sachs, M.D.
Senior Investigators
- Howard B. Dickler, M.D.
  Ronald E. Gress, M.D.
  Pierre A. Henkart, Ph.D.
  Kathleen Kelly, Ph.D.
  David M. Segal, Ph.D.
  J. Stephen Shaw, M.D.
  Gene M. Shearer, Ph.D.
  Alfred Singer, M.D.
  Dinah S. Singer, Ph.D.
  John R. Wunderlich, M.D.
- Immunotherapy Section—
  Richard J. Hodes, M.D.
- Transplantation Biology Section—
  David H. Sachs, M.D.
  Jeffrey A. Bluestone, Ph.D.

The Immunology Branch is concerned with the chemistry, genetics, biology, and clinical significance of immunity. Cellular immunity, transplantation immunity, and the nature of mammalian cell surfaces are the fundamental areas developed within the branch. Information derived from each of these areas is applied to studies of the relationship between the immune system and neoplastic cells in experimental animals and man.

Biochemical, biophysical, genetic, biological, and clinical investigative techniques are utilized in these studies.

Cellular Immunity—The cell-mediated immune responses of laboratory animals and human beings are being investigated. The responses studied *in vitro* include cellular proliferation, cell-mediated

cytotoxicity, and antibody production. Immune mechanisms which could be relevant for autologous neoplastic cell rejection are investigated. Immunity to chemically modified autologous cell-surface antigens, to autologous cells infected with influenza virus, immunity of F_1 hybrid cells to parental antigens, and cellular immune responses to cultured/syngeneic tumor cell lines represent the models under study. The role played by the major histocompatibility complex (MHC) both with respect to the MHC-product-associated immunogenic complexes found and to MHC as well as non-MHC immune response genes controlling reactivity to these immunogenic complexes is under investigation. The roles of the T-cell receptor and other accessory structures on T-cells are being analyzed in studies of conjugation and activation employing cloned as well as conventional T-cell populations.

The immunosuppressive events associated with and leading to the newly discovered acquired immune deficiency syndrome (AIDS) are being investigated by studying by the *in vivo* immune potential of human peripheral blood leukocytes, and by using *in vitro* and *in vivo* murine immune models. Particular emphasis is being placed on the possible synergistic effects of virus, exposure of the lymphoid system to sperm, and the suppressive and stimulatory signals associated with *in vivo* allogeneic lymphocyte reactions.

The nature of regulatory influences on the cell-mediated immune response to transplantation antigens is being investigated. Both synergizing and suppressive lymphoid subpopulations have been characterized in *in vitro* systems. Further work is being directed at the mechanisms of such regulatory influences, the role and expression of products of the *I* region of the MHC in these events, and the potential relevance to *in vivo* phenomena including transplantation and tumor immunity.

The mechanisms by which cytotoxic T lymphocytes and NK cells kill specific target cells are also under investigation. Cytoplasmic granules purified from these killer lymphocytes have been shown to be highly cytolytic. The role of these granules in cytotoxic lymphocyte mechanisms is being probed by molecular characterization of the granule components. The ability of the granule cytolysins to form pores in membranes is being studied using artifical membranes and protein biochemistry.

The receptors for immune complexes (Fc receptors) on different immunocompetent cell populations are being characterized by a variety of methods. The interactions of these receptors to antigens determined by the immune response gene region of the MHC (Ia antigens), surface IgM and IgD, as well as to other cell-surface molecules are being investigated. The role of this receptor and these interactions in the immune response and the regulatory role of antibody are currently being studied.

Humoral Immunity—A number of *in vitro* assays have been developed and characterized in the mouse including: primary and secondary antibody plaque-forming cell assays, T-cell proliferation assays, and antibody-secretion-enzyme linked immunoassay for use with a variety of antigens, including those under genetic control; and T-lymphocyte and accessory cell independent B-cell responses to antibodies specific for antigen receptors plus T-cell replacing factor(s). These assays are being used to evaluate the cellular level of expression of immune response genes and the mode of action of such genes; to evaluate the role of cell-surface antigens determined by the *I* region of the H-2 complex and the role of subpopulations of cells bearing these antigens; to characterize the nature and mechanism of action of antigen-specific helper and suppressor factors; to evaluate the immunologic role of idiotype-bearing molecules of both T- and B-lymphocyte origin; and to use purified factors and monoclonal antibodies to characterize the cell-surface molecules responsible for triggering and/or regulation of responses. Antibodies to idiotypic specificities of antibodies, the levels of which are regulated by immune-response genes, have been

shown to directly activate both helper T-lymphocytes and B-lymphocytes.

Transplantation Immunity—Antibodies against histocompatibility antigens and tumor antigens are used as reagents for determining the nature of these antigens and manipulating the immune response against them. Studies utilize inbred rats and mice and congenic mice. Strains of miniature swine have been developed as a model for organ transplantation studies.

Antibodies with specificities directed against transplantation antigens are being examined for chemical and immunologic individuality. Mouse lymphocyte alloantigens determined by genes in the *Ir* region (Ia antigens) are being studied serologically and functionally. Hybridomas producing monoclonal anti-H-2 and anti-Ia antibodies are being produced and characterized. Receptors of these antibodies are being examined for unique and for shared idiotypes.

Cytotoxic T lymphocyte clones are being generated and characterized. These clones are being used to study T cell receptors for MHC alloantigens.

Anti-idiotypic antibodies against mAbs and T cells are being used to modify immune responses to transplantation antigens.

Human allogeneic T-cell responses are being used as a probe to define new antigens in the HLA regions. Cloning of such T cells and their analysis with HLA-mutant cell lines allows precise genetic analysis. New gene products already defined by this approach are being studied for their relevance in regulating human immune responses and for association with human diseases.

New approaches to bone marrow transplantation are being explored. These include the use of monoclonal antibodies to eliminate GVH-producing donor cells. Such approaches are being evaluated in animal models and at the clinical level.

Immunochemistry—The structural and biological consequences of antigen-antibody interactions are being examined by using affinity cross-linked oligomers of IgG antibodies as models for naturally occurring immune complexes. The oligomers are being used to characterize immunoglobulin receptors on various cell types, to assess the effects of antibody polyvalency on cell binding, and to study the physiological consequences of the interactions of cross-linked immunoglobulins with cells. Affinity cross-linked oligomers are also being used to study the interaction of complement with IgG antibodies.

Tumor Immunology—Cellular immune mechanisms of tumor-bearing animals and patients with a variety of malignancies are studied, and attempts are made to modify reactions so as to improve tumor cell kill. Specific assays are established to determine the presence of humoral and cell-mediated responses of hosts to tumors.

Alternative assays are being tested for use in detecting early events in the recognition of malignant cells by host immune lymphoid cells. By means of such assays, attempts will be made to define at a structural level the characteristics of tumor cell-surface antigens which render these cells either susceptible or resistant to immune destruction in the tumor-bearing hosts.

Immunotherapy of tumors is approached both in animal models and patients using nonspecific and specific stimulation of the immune system. A clinical study is in progress to evaluate the effectiveness of adjuvant therapy in preventing recurrence of malignant melanoma in patients who have been rendered clinically free of disease but who have poor prognosis in the absence of therapy. Comparison is being made between adjuvant chemotherapy with methyl-CCNU and immunotherapy with either BCG alone or BCG plus a vaccine of neuraminidase-treated allogeneic melanoma cells.

Molecular Immunology

The molecular mechanisms that regulate the expression and synthesis of histocompatibility genes are currently being investigated. Using recombinant DNA technology, individual members of the MHC multigene family have been isolated. Analysis of their primary DNA se-

quences is in progress in order to investigate mechanisms generating diversity. Introduction of isolated MHC genes into cells results in the expression of the heterologous MHC antigen on the host cell surface, providing a system in which to study the regulation of expression of these MHC genes. Such transfected MHC gene is subject to regulatory constraints indistinguishable from those of endogenous MHC genes. For example, interferon treatment of the transformed cells resulted in enhanced transcription of both heterologous and endogenous MHC genes. Current efforts are directed toward identifying cellular and extracellular factors which affect MHC gene expression. Such studies should shed light on the effect of modulation of MHC antigen expression on immune mechanisms during disease processes. Isolated MHC genes have also been introduced into mice by microinjection. These transgenic mice will be useful in the study of MHC gene regulation, recognition of xenogeneic MHC molecules, and modulation of transplantation immunity by gene therapy.

The regulation of lymphocyte proliferation is being examined through an analysis of gene sequences that are induced during lymphocyte activation. Such sequences are being isolated from human lymphocytes by cDNA cloning and will be analyzed functionally by DNA-mediated gene transfer. It is expected that by defining the genes that are regulated in parallel with growth, insight will be gained into the regulation of the immune response and the deregulation that occurs in malignant growth.

Metabolism Branch—
Thomas A. Waldmann, M.D.

- Cellular Immunology Section—
  R. Michael Blaese, M.D.
- Endocrine Section—
  James M. Phang, M.D.

The Metabolism Branch is broadly concerned with clinical and laboratory studies that focus on the immunologic, endocrinologic, and metabolic basis of disease occurring in patients with neoplasia.

Immunologic interests encompass a broad area of immunological investigations. These studies are directed toward defining the factors involved in the control of the human immune response.

Major efforts in this area are directed toward: studies of the arrangement of immunoglobulin genes and the genes encoding the antigen-specific T-cell receptor and the gene rearrangements and deletions that are involved in the control of immunoglobulin synthesis; and the antigen-specific T-cell receptor, the genetic control of the immune response especially as related to immune response genes including the relationship between HLA antigens and disease and genetic factors controlling the response to complex chemically defined proteins; identification of unique cell surface determinants, especially receptors for growth factors on subpopulations of lymphoid cells with different functional capabilities using antibodies developed with hybridoma technology; characterization of the function and structure of the receptor for interleukin-2 and cloning of the gene for this inducible cell surface receptor; analysis of action of immunoregulatory cells including helper T cells, suppressor T cells and macrophages that regulate antibody responses and on studies of disorders of these immunoregulatory cell interactions in patients with immune dysfunction; studies of the immune response including the generation of specific antibodies and cytotoxic cells to viruses; the isolation and characterization of biological modifiers that suppress the human immune response that are produced *in vivo* or by T cell lines and T-T cell hybridomas; and studies of immune regulation, including factors controlling helper and suppressor T-cell function immunodeficiency states (hypogammaglobulinemia, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia telangiectasia), and leukemias of T-cells, as well as in animal models of disordered immunity.

Endocrine interests include biochemical studies of amino acid metabolism related to collagen synthesis and gluconeogenesis

(studies of regulation of enzymes in the collagen synthetic pathway and the proline degradative pathway). These are related to studies of patients with disorders of metabolic bone disease, diabetes mellitus, and amino-acidopathies. Studies of growth hormone, somatomedin I and II, and other growth peptides and their cellular receptors are related to studies of patients with growth disorders.

Basic Research Laboratories

Laboratory of Biochemistry—
Maxine Singer, Ph.D.

The emphasis of the work in the laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development, and differentiation. The study of regulation encompasses regulation of gene expression, regulation by interaction of macromolecules, and regulation of cells by hormones and ions. Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology, and molecular genetics.

- Biosynthesis Section—
  Edward L. Kuff, M.D., Ph.D.

Studies on the evolution and functional significance of endogenous retroviral genetic elements, the enzymatic mechanism of DNA synthesis, and the regulation of collagen biosynthesis and secretion in normal and transformed cells are the concern of this section. Technical approaches include analysis of nucleic acid sequence relationships and genomic organization, isolation of subcellular and viral components, purification of DNA polymerases and their use in constructing *in vitro* synthetic systems, and the characterization of enzymes and cofactors involved in sequential processing of newly formed collagen.

- Cellular Regulation Section—
  O. Wesley McBride, M.D.

Regulation and control of gene expression in eukaryotes is studied using bovine papilloma virus and simian virus 40 as vectors for animal cells and yeast plasmids. Expression vectors are constructed using recombinant DNA techniques, and control of gene expression is evaluated at the levels of both transcription and translation. In other studies, chromosome- and DNA-mediated gene transfer into heterologous mammalian cells is used to map human genes and to isolate restricted regions of the human genome. Somatic cell hybrids are employed to map various human genes, including immunoglobulin genes, to specific chromosome segments.

- Developmental Biochemistry and Genetics Section—
  Michael Yarmolinsky, Ph.D., Acting

Studies on the biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The structure of selected components of the genome of several animal species is studied, as a basis for analyzing the regulation of gene expression during the development of germ cells and embryos. Currently under study are the functional significance of the organization of chromatin in *Drosophila* and genes encoding muscle-specific proteins in chickens. The regulation of DNA synthesis in the cell cycle is studied in prokaryotes, phage and plasmids.

- Macromolecular Interactions—
  Claude B. Klee, M.D.

Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+}, calmodulin, and cyclic nucleotides. Enzymes regulated by calmodulin are characterized, and then interaction with calmodulin and other regulatory ligands are studied at the molecular level as well as in eukaryotic cells in tissue culture.

• Nucleic Acid Enzymology Section—
Maxine Singer, Ph.D.

Studies pertain to a variety of nucleic acid structural and functional relationships in eukaryotic cells and viruses. Of particular interest is the organization and function of repetitive sequences in primate DNA, and the study of centromeric structure/function relations.

• Protein Chemistry Section—
Elbert A. Peterson, Ph.D.

Studies are in progress on the biochemical changes accompanying differentiation and maturation of leukocytes and the nature of factors controlling these processes; the interactions between cells involved in the immune response and the identification and isolation of participating cell types; and the development of new physical and immunological methods for the purification of cell populations, subcellular organelles, and proteins.

Laboratory of Cell Biology—
Lloyd W. Law, Ph.D

• Office of the Chief

The laboratory conducts investigations to identify and characterize, and to isolate and purify, tumor specific antigens using model systems in experimental animals. These studies require the use of immunologic, biochemical, somatic cell hybridization, gene cloning and monoclonal antibody production techniques. Studies include immunologic responses to tumor specific antigens both solubilized and soluble, obtained from spontaneous, chemically and virally induced neoplasms. Studies also involve identification of the genetic elements involved in tumorigenesis and in the induction of tumor specific antigens and the relationship between tumor induction and tumor antigens, using transfection techniques.

• Chemistry Section—
Ettore Appella, M.D.

This section focuses on different aspects of chemical immunology. One aim is to define the molecular nature of the unique transplantation antigens found among different tumors. This study involves the biochemical purification of such antigens, their chemical structure and gene cloning, and their role in tumor rejection. A second aspect is an investigation of the role played by the Class I and Class II histocompatibility antigens, both in the recognition of different antigens and the control of malignancy. This is being approached by site-directed chemical mutagenesis of cloned histocompatibility genes and expression of the mutant gene in L-cells. A third investigation is a basic approach to the problem of growth control by different transforming proteins using chemical synthesis.

Laboratory of Immunobiology—
Tibor Borsos, Sc.D.

• Cellular Immunity Section—
Berton Zbar, M.D.

The section evaluates the efficacy of immunological methods for inhibition of tumor growth in animal models. Antitumor activity of plasma absorbed against protein A-Sepharose and Sepharose derivatives is being evaluated in rats with primary mammary cancer and immunochemical studies are performed to identify the molecules in absorbed plasmas that possess antitumor activity. The nature of the interaction between murine retroviruses and guinea pig tumor cells is studied; heterogeneity of viral phenotype in cells infected with murine leukemia viruses, the consequences of this heterogeneity *in vivo* and the genetic basis of the heterogeneity in viral phenotype are studied. The efficacy of retroviral vaccines will be evaluated in animal models. These studies make use of the techniques of molecular biology.

• Office of the Chief
Tibor Borsos, Sc.D.

Antibody- and complement-mediated cytotoxic reactions are studied for the mechanism of action. The primary goal is to understand the molecular basis of complement action and the molecular basis of cell defense mechanism against complement attack. Purification of antibodies, complement components, cell membrane receptors, and studies of synthetic pathways that control cell membrane integrity are also part of the study.

- Immunopathology Section—
  Edward J. Leonard, M.D.

The main goal of this section is to understand the basis for leukocyte accumulation at sites of inflammation. Cell biology and biochemistry of chemotaxis are studied. Methods including protein purification, flow cytometry, monoclonal antibody generation, chemotaxis assays and toxic metabolite measurement are used to identify chemotactic factors, enumerate cell surface receptors, and study chemotactic stimulus-response pathways. *In vitro*, animal and human experiments are performed.

Laboratory of Molecular Biology—
Ira Pastan, M.D.

- Molecular Biology Section—
  Ira Pastan, M.D.

This section studies how hormones, viruses, and toxins enter cells and how intracellular sorting and processing of these molecules occurs. This information is currently being applied to new methods of cancer treatment using monoclonal antibodies and immunotoxins. Studies are also carried out on how drugs used in cancer treatment enter cells and on the molecular and biochemical basis of drug resistance in human cancer. Using molecular cloning techniques, the structure and function of genes encoding receptors for hormones and growth factors is being studied. Biochemical experiments are carried out on how transforming proteins such as the transforming protein of Rous sarcoma virus, $p60^{src}$, control cell behavior, cell growth, and gene expression.

- Biochemical Genetics Section—
  Susan Gottesman, M.D.

This section studies the regulation of gene expression in *E. coli* and the bacteriophage lambda, including analyses of the control of transcription initiation, transcription termination, and the role of protein stability in regulation of cell division in bacteria; DNA replication and recombination in prokaryotes with emphasis on site-specific recombination by the bacteriophage lambda replication.

- Gene Regulation Section—
  Benoit de Crombrugghe, M.D.

This section studies the developmental control of eukaryotic genes including the identification of their regulatory signals, the genetic and biochemical characterizations of their control mechanisms and the effects of transforming proteins on their expression. Particular emphasis is placed on the collagen genes, a family of developmentally regulated genes. Methods include DNA cloning, gene transfer and selection of mutants.

- Ultrastructural Cytochemistry Section—
  Mark Willingham, M.D.

This section focuses on the study of basic cellular mechanisms of cell and organelle movement and function using morphologic techniques, especially electron and light microscopic immunocytochemistry, image intensification microscopy of living cells, and direct microinjection of single cells in tissue culture.

- Membrane Biochemistry Section—
  Kenneth Yamada, M.D., Ph.D.

The structure and function of plasma membrane and extracellular glycoproteins such as fibronectin are examined by biochemical, immunological, and cell biological approaches using normal and malignant cells.

- Developmental Genetics Section—
  Sankar Adhya, Ph.D.

To elucidate the mechanisms of control of gene expression in prokaryotes, genetic and biochemical experiments are conducted to determine how various regulatory molecules function to modulate transcription and/or translation.

- Molecular Cell Genetics Section—
  Michael Gottesman, M.D.

Molecular and somatic cell genetic approaches are used to analyze malignant transformation, growth control, cytoarchitecture, and drug resistance of cultured cells. Techniques employed include mutant isolation, somatic cell hybridization, gene transfer, and molecular cloning.

- Molecular Genetics Section—
  Bruce Howard, M.D.

Research focuses on development and application of techniques for introducing

genetic material into mammalian cells. Emphasis is placed on isolation of genes that control cell growth, with the goal of understanding how abnormal expression of such genes may contribute to malignant transformation and cellular senescence.

Laboratory of Pathology—
Lance A. Liotta, M.D., Ph.D.

- Surgical Pathology and Postmortem Section—Ernest E. Lack, M.D.
- Hematopathology Section—Elaine S. Jaffe, M.D.
- Cytopathology Section—Elizabeth W. Chu, M.D.
- Tumor Invasion and Metastases Section—Lance A. Liotta, M.D., Ph.D.
- Biochemical Pathology Section—David A. Zopf, M.D.
- Ultrastructural Pathology Section—Timothy J. Triche, M.D., Ph.D.

The Laboratory of Pathology of the National Cancer Institute offers a 2- to 3-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. The research activities of the staff are varied, and participation in clinical or basic research projects is an intrinsic part of the program during elective periods. Research interests of the laboratory include: viral oncology, molecular biology, immunopathology, immunochemistry, mechanisms of metastasis, comparative oncology, and tumor biology.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of the biochemistry and molecular genetics of cancer invasion and metastases, cell surface biochemistry of lymphocytes, oncogene growth regulation in neoplastic cells, gene rearrangements in lymphomas, ultrastructural studies of neoplastic cells, and receptor biology.

Laboratory of Mathematical Biology—
Jacob V. Maizel, Jr., Ph.D.

The activities of the Laboratory of Mathematical Biology fall into several broad areas: macromolecular structure and function, membrane structure and function, immunology, pharmacokinetics, and computational and modeling methodology. The work is both theoretical and experimental. Application of theoretical understanding to these biological systems, which serve as models for aspects of the cancer process, is accomplished through the use of advanced computing. Close collaboration provides valuable feedback and knowledge transfer between these two research domains. The laboratory consequently develops computer methodology that is utilized by researchers of the entire biomedical community.

- Molecular Virology—Jacob V. Maizel, Jr., Ph.D.

Human viruses are studied with the goal of understanding the molecular mechanisms, replication, synthesis, assembly, and interaction of viral genome--encoded macromolecules with the architecture and functions of their host cells. It is our goal to understand virus-cell systems through computer analysis, experimental molecular biology, and genetic engineering. General principles are found that are applicable to other human cellular systems since viruses depend on the cells almost entirely for their major biochemical machinery. In the past findings from viral systems have led to discoveries concerning assembly of cell architectural elements, splicing of pre-mRNAs, nuclear--cytoplasmic interactions, and the associations between viral and cellular proteins involved in cell transformation. As a long-term goal we aim to define these systems in terms of the sequences of their genomes and the computed properties of the molecules encoded by them.

- Membrane Structure and Function—Robert P. Blumenthal, Ph.D.

This investigates the dynamics of membrane components (lipids, proteins) in biological membranes and in reconstituted lipid-protein systems using a variety of biophysical techniques. Current studies

examine properties of ion channels inserted into planar bilayers and mechanisms of membrane fusion mediated by viral spike glycoprotein reconstituted into lipid vesicles.

- Molecular Structure and Properties
  Robert L. Jernigan, Ph.D.

Biopolymers and their conformations and properties are investigated from a theoretical viewpoint. In the basic research, new methods are developed to treat problems of current interest in molecular biology. Applications, typically computer intensive, are globular proteins, membrane proteins, structural proteins, and DNA-protein binding.

- Theoretical Immunology—
  John N. Weinstein, M.D., Ph.D.

Monoclonal antibodies as well as other "biologicals", are investigated by a combination of experimental and theoretical approaches for diagnosis and treatment of cancer. The approach is eclectic, involving membrane biophysics and biochemistry, immunochemistry, *in vitro* cell studies, *in vivo* animal pharmacology, clinical protocols and theoretical modeling, molecular structure analysis, and molecular graphics.

- Image Processing—
  Lewis E. Lipkin, Ph.D.

The Image Processing Section works in the areas of nucleic acid structure, 2-D gel protein analysis and computer controlled and/or aided microscopy. This work is facilitated by several dedicated large minicomputers and a dedicated mainframe.

- Membrane Biology Section—
  Pedro Pinto da Silva, Ph.D.

Our work proceeds along these main areas:

I. Structure and dynamics of plasma and intracellular membranes: we develop and apply new combinations of freeze-fracture and cytochemical techniques ("fracture-label" and "label-fracture") to study the partition and surface distribution of membrane lipids and proteins.

II. Intermolecular distances in the cytoplasm and nucleoplasm: we develop and apply a new technique, "fracture-permeation", to assess the degree of compactness of the cytoplasm and nucleoplasm in glutaraldehyde fixed cells.

III. Membrane fusion; structure and biogenesis of intercellular junctions: we study the freeze-fracture morphology of cellular processes that involve membrane fusion (e.g., exocytosis). We study also the morphology of specialized intercellular contacts—tight and gap junctions—viewed as stabilized intermediates of fusion between components of adjacent plasma membranes in eukaryotic cells.

Laboratory of Genetics—
Michael Potter, M.D.

Much of the focus of research is on the role of genes that determine susceptibility and resistance to neoplastic development and special genes and their products that are associated with the neoplastic state (oncogenes, retroviral gene products, tumor associated antigens). The laboratory has had a long association with the study of the plasma cell tumor system in mice. Research continues on the organization of immunoglobulin genes, and gene families and structure function correlations with monoclonal antibodies.

Current ongoing projects concern: expression of the myc (and other) oncogenes in lymphomas and plasmacytomas; immunoglobulin V_K and V_H gene families in the genus *Mus*; structure and identification of contact amino acids in phosphorylcholine; lysozyme and galactan binding monoclonal antibodies; pathogenesis of erythroleukemia in mice; thyroglobulin producing cell lines; isolation and characterization of unique tumor associated antigens; and the search for genes that control susceptibility to plasmacytomagenesis in BALB/c mice.

The laboratory can provide research training in amino acid and DNA sequences, recombinant DNA technology, tissue culture, hybridoma-monoclonal and antibody production.

Laboratory of Tumor Immunology and Biology—
Jeffrey Schlom, Ph.D.

The laboratory conducts research to identify immunologic markers specific for, or associated with, various human neoplasms, with the ultimate aim of applying these toward the diagnosis, prognosis, and treatment of human

cancer. Specifically, the laboratory is engaged in studies involving the generation and characterization of monoclonal antibodies to tumor associated determinants with particular emphasis on the study of human carcinomas. Studies ongoing involve the conjugation of monoclonal antibodies to isotopes or toxins, to aid in the diagnosis, localization, and potentially the elimination of tumor cells. Immunoassays are being developed that will aid in the characterization of human tumor cell populations, and in the diagnosis or prognosis of certain human cancers. The laboratory is also engaged in studies to investigate the association between specific murine and human genetic elements and tumorigenesis, employing techniques of gene cloning and molecular hybridization.

- Experimental Oncology Section—Jeffrey Schlom, Ph.D.

Projects under way include research to generate and characterize monoclonal antibodies that are reactive with mammalian carcinoma cells with emphasis on human breast and colon carcinomas; to use monoclonal antibodies to identify and characterize specific proteins that are associated with the neoplastic state, with emphasis on human carcinoma systems; and to develop immunoassays that will aid in the characterization of human carcinoma cell populations and in the diagnosis or prognosis of human carcinomas. The use of monoclonal antibody, conjugated with isotopes, is being investigated to aid in the detection or therapy of carcinoma lesions. Experiments are being conducted to determine those factors which influence the antigenic modulation, antigenic phenotype, and the state of differentiation of human carcinoma cell populations.

- Oncogenetics Section—Robert Callahan, Ph.D.

This section seeks to identify and molecularly clone tumor specific cellular and viral genetic elements from human carcinoma and other mammalian tumors. Research is being conducted to determine the organization of tumor specific genetic elements in cellular DNA, and the biological activity and role of tumor specific genes in normal and neoplastic tissue. The ultimate aim is to develop an understanding of the genetic changes which are relevant to the etiology of human neoplasia.

- Biochemistry of Oncogenes Section—Robert Bassin, Ph.D.

Investigations of the mechanisms of cellular transformation mediated by RNA tumor viruses and by related cellular oncogenes are under way, emphasizing the nature and functions of specific cellular proteins which are involved in the transformation process. Studies are being conducted to identify genetic elements responsible for tumorigenesis and for immunologic markers specific for various human carcinomas. Studies are also being carried out to investigate the cellular control mechanisms which are active in preventing infection and disease by endogenous RNA tumor viruses.

- Cellular and Molecular Physiology Section—Herbert L. Cooper, M.D.

This section plans and conducts research on the mechanisms regulating synthesis and posttranslational modification of proteins in normal and malignant cells in order to detect, characterize, and exploit specific regulatory defects of protein synthesis associated with neoplasia. Studies are in progress to investigate biochemical events involved in the synthesis, immunological function, and role in intercellular interactions of membrane-associated proteins. Modulation of synthesis and expression of these proteins in relation to the malignant state will be emphasized. Physiological and biochemical events related to cellular differentiation in the response of normal and neoplastic cells to tumor-promoting and -suppressing substances are also being studied.

- Cell Cycle Regulation Section—William R. Kidwell, Ph.D.

The program of this section focuses on the role of growth factor production by human mammary tumor cells in tumor initiation, growth and progression. Four growth factors have been purified from breast tumors. One of these acts on

breast cells to promote synthesis of the basement membrane, a natural barrier against tumor invasion. This factor is high in well differentiated tumors and absent from metastatic tumors that do not make a basement membrane. Three other growth factors detected act synergistically to promote anchorage-independent growth, a characteristic of transformed cells. Studies underway are designed to characterize the receptors for these factors on tumor cells, to elucidate the mechanisms regulating expression of growth factors by different tumor types, and to determine whether the levels of the growth factors in tumors can be exploited for diagnostic, prognostic or therapeutic purposes for the treatment of breast cancer. Laboratory techniques include methods for breast cell culture, protein purification and characterization, immunological and biochemical analyses, and gene cloning.

- Cellular Biochemistry Section—
  Yoon S. Cho-Chung, M.D., Ph.D.

This section studies the cellular mechanisms regulating the growth and regression of neoplasms. Emphasis is placed on the roles of cyclic nucleotides, hormones and other intracellular mediators in the growth control of normal and neoplastic cells. Current studies involve the roles of cyclic AMP and estrogen in the regulation of the expression of cellular proto-oncogenes, especially the c-*ras* gene in the established mammary carcinomas as well as during mammary carcinogenesis. The ultimate aim of these studies is to apply these toward the diagnosis, treatment and prevention of human cancer.

Laboratory of Cellular Oncology—
Douglas R. Lowy, M.D.
Senior Investigators

- Kenneth S. S. Chang, M.D.
  Nelson A. Wivel, M.D.
  Stringer Sue Yang, Ph.D.

The Laboratory of Cellular Oncology actively supports training physicians and other scientists in experimental approaches to the study of tumor biology. Initial Staff Fellowship appointments are for two years, with the possibility of renewal. Specific research projects are developed jointly by the Staff Fellow and his or her supervisor. These choices are based on the long-term objectives of the Fellow and the research interests and expertise of the Laboratory. Fellows participate fully in the Laboratory's regular meetings that discuss current journal articles, analyze data obtained by investigators in the Laboratory, and present speakers from outside the Laboratory. For Dermatologists in training, a combined clinical and research program (with up to one year of Residency credit towards Board eligibility) is available in conjunction with the Dermatology Branch, NCI.

The Laboratory carries out research on the genetics and immunology of oncogenesis. The studies seek to identify critical differences between normal and neoplastic cells. The purpose of these investigations is to acquire information that may ultimately lead to improved diagnosis, therapy, or prophylaxis of neoplastic diseases.

Investigators in the Laboratory probe the mechanisms by which normal cells become neoplastic through studying the effects of viral and cellular transforming genes (oncogenes) on tissue culture cells or experimental animals. Alteration of tumor growth patterns by the immune system and by biological modifiers such as interferon is also studied. Tumor virus systems utilized in the Laboratory include polyomaviruses and papilloma-viruses, rodent and primate retroviruses, and acute transforming retroviruses. The structure and function of viral and cellular *ras* transforming genes has been the focus of many studies in the Laboratory. Current efforts in this area seek to define the role of transforming genes in spontaneous tumors.

A wide range of experimental techniques are employed in carrying out these studies. These include gene cloning by recombinant DNA technology, DNA mediated gene transfer, morphological transformation of tissue culture cells, quantitative virological assays, fractionation of sub-cellular components, radioimmunoassays, molecular hybridization, and *in vitro* mutagenesis.

Division of Cancer Etiology, NCI

Richard H. Adamson, Ph.D., Director

The Division of Cancer Etiology plans and directs laboratory, field and epidemiologic and biometric research on the cause and history of cancer. It studies prevention of cancer through direct intramural research, research grants and contracts; evaluates mechanisms of cancer induction and promotion by chemicals, viruses and environmental agents; serves as the focal point for the federal government on the synthesis of clinical, epidemiological, and experimental data relating to cancer causation; and advises the Institute Director on basic research activities as they relate to cancer cause and prevention. The intramural program conducts a basic laboratory research program on the causes of cancer by chemical, physical, and biological (viral) factors; and on the pathogenesis and prevention of various cancers.

Laboratory of Biology—

Joseph A. DiPaolo, Ph.D.

The Laboratory of Biology is primarily interested in the modulation of the transformation process that leads to malignancy. The primary objective is to determine the crucial molecular and physiological changes that occur in cells which have been treated with chemical or physical agents as they transform from the normal to the neoplastic state. The laboratory uses biological preparations, cells from animals and humans and a variety of intact mammals. The present emphasis is the study of oncogenes and DNA changes which are responsible for the activation of genes in neoplasia. Concurrently, the role of growth factors, in particular, leukoregulin, a hormone which is noncytotoxic to normal cells and is capable of inhibiting the transformation process, is being investigated in terms of its cell receptor and interaction with other physiological agents during carcinogenesis.

Laboratory of Experimental Carcinogenesis

Snorri S. Thorgeirsson, M.D., Ph.D.

The Laboratory of Experimental Carcinogenesis plans, develops, and implements a research program to elucidate mechanism(s) of malignant transformation in human and animal cells by chemical carcinogens and other cancer causing agents; to determine critical cellular and genetic factors involved in initiation, promotion and progression of these transformed cells, and to apply, whenever possible, the knowledge obtained from these studies towards effective prevention of cancer in man. Studies are designed to (1) identify and characterize exogenous and endogenous factors controlling initiation, promotion and progression of chemically induced tumors; (2) elucidate the regulation of gene expression and differentiation in both human and animal neoplasia; (3) define the mechanism by which modifiers of cellular differentiation may inhibit and/or promote the neoplastic process; and (4) characterize the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines.

Laboratory of Comparative Carcinogenesis

Jerry M. Rice, Ph.D.

The Laboratory of Comparative Carcinogenesis plans, develops, and conducts a research program to compare effects of chemical carcinogens in rodents and in nonhuman primates in order to identify differences between species that are of importance for interspecies extrapolations of the effects of chemical agents, including extrapolations to man, and that afford experimental approaches to the elucidation of mechanisms in chemical carcinogenesis. The research of the Laboratory is oriented toward identification of susceptibility and of resistance to chemical carcinogenesis, and toward identification, description, and investigation of mechanisms for interspecies differences and for cell and organ specificity in chemical carcinogenesis. The Laboratory investigates the roles of nutrition, meta-

bolism, the perinatal age period, and pregnancy in modifying susceptibility to chemical carcinogens, and conducts biologic and morphologic studies on the pathogenesis of naturally occurring and induced tumors in experimental animals.

The Laboratory consists of five sections: Tumor Pathology and Pathogenesis Section, Ultrastructural Studies Section, Nutrition and Metabolism Section, Chemistry Section, and Perinatal Carcinogenesis Section. In addition, there are research working groups on nonhuman primates, inorganic carcinogens, and developmental biology within the Office of the Chief. Major areas of research within the Laboratory include studies on transplacental chemical carcinogenesis in rodents and in nonhuman primates; the relation of morphogenetic differentiation to prenatal susceptibility to carcinogens; identification of tumor promoters through in vivo experimentation; mechanisms underlying cellular specificity, as well as dose/effect relationship, for tumor promotion in internal organs in different species including nonhuman primates; investigations of carcinogenesis by toxic metals; characterization and histogenetic studies of experimental tumors by immunochemistry and histochemistry, and by light electron microscopy; and mechanisms underlying the organ-specific carcinogenic properties of major classes of chemical carcinogens including N-nitroso compounds.

Laboratory of Cellular and Molecular Biology—
Stuart A. Aaronson, M.D.

The Laboratory of Cellular and Molecular Biology directs a comprehensive research program to (1) identify, isolate and characterize the transforming genes of acute transforming retroviruses; (2) elucidate the molecular mechanisms of transformation by retroviruses and retroviral *onc* genes; (3) determine the role of cellular DNA analogues of retroviral transforming genes in naturally occurring malignancies of human and other species; (4) identify, isolate and characterize transforming genes of human tumor cells; (5) elucidate the mechanisms by which replication-competent type C viruses cause leukemia; (6) search for new mammalian retroviruses and establish their origins and evolutionary relationships to known oncoviruses; (7) apply techniques developed in the investigation of naturally occurring and virus-induced cancers of animals to the search for viral etiology of human tumors; and (8) analyzes the effect of environmental agents or specific mechanisms which control and promote transformation in mammalian cells.

Laboratory of Cellular Carcinogenesis and Tumor Promotion—
Stuart Yuspa, M.D.

The Laboratory of Cellular Carcinogenesis and Tumor Promotion plans, develops and implements a comprehensive research program to determine the molecular and biological changes which occur at the cellular and tissue levels during the process of carcinogenesis. Studies are designed to define normal regulatory mechanisms for cellular growth and differentiation; determine the mechanism by which carcinogens alter normal regulation and the biological nature of these alterations; investigate the mechanism by which tumor promoters enhance the expression of carcinogen-induced alterations; identify cellular determinants for enhanced susceptibility or resistance to carcinogens and tumor promoters; and elucidate the mechanism by which certain pharmacologic agents inhibit carcinogenesis.

The laboratory is composed of three sections, each of which is charged with a major responsibility for portions of the laboratory goals. Because of the integrated approach toward an understanding of mechanisms of carcinogenesis, considerable interaction occurs among the sections.

- The *In Vitro* Pathogenesis Section—
  Stuart Yuspa, M.D.

  This section develops relevant model systems for the study of all phases of the process of carcinogenesis; defines regulatory mechanisms for the normal control of growth and differentiation and alterations in these controls induced by initiators and promoters; clones and characterizes genes involved in differen-

tiating of normal and tumor cells; studies functional alterations in gene expression produced by initiators and promoters and the mechanism by which these functional changes occur; and elucidates factors which determine susceptibility to carcinogenesis.

- The Differentiation Control Section—Luigi DeLuca, Ph.D.

This section studies the biological and biochemical factors involved in normal differentiation of epithelial tissues; uses pharmacological techniques to alter differentiation of normal, preneoplastic and neoplastic epithelial cells to determine the relevance of differentiation to carcinogenesis and to determine methods to intervene in preneoplastic progression; studies the relationship between differentiation and growth control; and focuses on cell surface changes in differentiation and neoplasia.

- The Molecular Mechanisms of Tumor Promotion Section—Peter Blumberg, Ph.D.

This section studies the interaction of promoters with specific cellular receptors; elucidates the functional importance of receptors in promoter action; identifies endogenous ligands with specific affinity for receptors of exogenous promoters; and characterizes the initial biochemical steps in the cascades associated with receptor occupancy. Particular attention is focused on the major target of phorbol ester action, protein Kinase C. In approaching these goals, the laboratory utilizes the latest technology in cell and molecular biology, as well as biochemical, pharmacological and immunological methods.

Laboratory of Experimental Pathology—Umberto Saffiotti, M.D.

This laboratory focuses on the study of neoplastic transformation and its underlying mechanisms, with particular emphasis on epithelial target cells. It plans, develops and implements research on the experimental pathology of carcinogenesis, especially concerned with the induction of neoplasia by chemical and physical factors in epithelial tissues, including: development, characterization and evaluation of experimental pathology models of human cancer, such as cancers of the respiratory tract, by *in vivo* and *in vitro* carcinogenesis methods; development and characterization of tissue culture systems for quantitative study of the effects of carcinogens alone or in combination; and research on mechanisms of carcinogenesis correlating different levels of biological organization, from whole organisms (human and animal), organs and tissue, to the cellular, subcellular and molecular levels.

Chemical carcinogenesis mechanisms are studied in various cellular model systems. Quantitative relationships are investigated for different end-points such as cytotoxicity, DNA damage, mutation and transformation. DNA-mediated gene transfer is used to identify the diversity of transforming genes activated by chemical carcinogens and co-factors. Molecular biology studies are addressed to the characterization of new transforming genes and to the investigation of DNA regions that may have particular specificity for interacting with carcinogens. Metabolism and interactions are studied for several known or suspected carcinogens. Other studies related to transformation mechanisms include the induction of collagenalytic activity for invasiveness and modifications in bioenergetic pathways.

- Respiratory Carcinogenesis Section—Umberto Saffiotti, M.D.

In vivo studies of multifactorial carcinogenesis in the respiratory tract by organic and inorganic chemicals, particulate materials and physical factors are paralleled by studies on the underlying cellular mechanisms of cell proliferation and differentiation, and by studies of the cells of origin of tumors *in vivo* and in culture.

- Tissue Culture Section—M.E. Kaighn, Ph.D.

Chemically defined, serum-free culture methods are developed to provide optimal conditions for growth, differentiation and neoplastic transformation of epithelial cell systems; current studies are

on epidermal, respiratory and prostate epithelial cells. Mechanisms involved in the control of cell differentiation, transformation, and gene activation are investigated in collaboration with other parts of the laboratory.

Laboratory of Human Carcinogenesis—Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess (a) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, (b) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation; and (c) host factors that determine differences in carcinogenic susceptibility among individuals.

Molecular and Biochemical Epidemiology—Measurement of gene polymorphism by molecular approaches, e.g., DNA polymorphism, to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens.

Carcinogen Macromolecular Interaction—Activation of cellular oncogenes by carcinogens; identification of metabolic pathways of carcinogen activation and deactivation; inter- and intragenic damage and rearrangements caused by chemical and physical carcinogens; and determination of the importance of repair of carcinogen-induced damage to DNA and chromosomes in carcinogenesis.

In Vitro Carcinogenesis—Investigation of the mechanisms of neoplastic transformation; role of oncogenes in human cell carcinogenesis; studies of phenotypic and genetic alterations during *in vitro* carcinogenesis; assessment of the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and identification of extra-, inter-, and intra-cellular factors modulating growth and differentiation of human epithelial cells.

Laboratory of Molecular Carcinogenesis
Harry V. Gelboin, Ph.D.

The goal of the Laboratory of Molecular Carcinogenesis is an increased understanding of the cellular and biochemical events and mechanisms involved in carcinogenesis: a study of various aspects of initiation and promotion by chemicals in tissue culture, with emphasis on mutation and the consequences of altered cellular proteins, especially actin. DNA transfection and sequencing are used to define the genomic changes observed; examination of the unusual properties of cells from patients who may be pre-disposed to cancer because of hereditary disease, and an investigation of various mechanisms of DNA repair. Emphasis is placed on DNA repair properties of malignant human cells; investigation of the genetics, multiplicity, and structure of the drug and carcinogen metabolizing enzyme systems. Monoclonal antibodies are used to gain an understanding of individual differences and their relationship to drug and carcinogen sensitivity; shuttle vectors which replicate in mammalian and bacterial cells are used to study the mutation, recombination, and repair caused by carcinogen treatment. Genetic stability of the genome under various circumstances is evaluated by DNA sequencing; a study on the temporal control of events in the cell-cycle of normal and malignant cells. Synchronized cell populations are used; and a study of the relationship between structure and function in chromatin, using biochemical and immunological methods, including evaluation of the regulatory properties of the non-histone proteins.

Laboratory of Molecular Oncology
Takis S. Papas, Ph.D.

This section plans and conducts research on the molecular elements responsible for the development and expression of malignant phenotypes in humans and animals; and applies skills in molecular biology, recombinant DNA technology and hybridoma-monoclonal

antibody production in a comprehensive program to identify and isolate cellular transforming genes and to characterize products expressed by these genes.

- Microbiology Section—
  Donald G. Blair, Ph.D.

This section is concerned with the biological analysis of oncogenes in human and non-human genomes, and in the development of biological assays using animal models and tissue culture techniques to detect and isolate such genes and to determine the factors necessary for them to cause neoplastic transformation and tumor growth.

- Carcinogenesis Regulation Section—
  Takis S. Papas, Ph.D.

This section studies the relationship between oncogenic viral gene expression and the conversion of cells from normal to transformed phenotype; and tests specific regions of molecular cloned acute transforming retroviruses for transforming activity and elucidates the molecular mechanisms of interaction with the cell.

- Cellular Transformation Section—
  John P. Bader, Ph.D.

This section identifies virus-coded protein responsible for the malignant transformation of cells by Rous sarcoma virus; determines the biochemical function of this protein; determines the primary physiological effects resulting from the functioning of this protein; describes the sequence of metabolic changes which result in the altered metabolic profile characteristic of malignant cells; and distinguishes metabolic changes necessary for the maintenance of the malignant state.

- Molecular Control and Genetics
  Section—Donald L. Court, Ph.D.

This section conducts studies to understand how gene expression is controlled in the prokaryote, *E. coli,* and its phage lambda. The molecular basis of gene regulation is determined at the level of transcription initiation, transcription termination, RNA translation, and RNA processing. These studies are being developed to understand the eukaryotic systems and to resolve the intricate regulatory and control mechanisms for this latter, more complex system at the molecular genetic level. Additionally, this section helps to develop the vectors and expression constructs required for the Laboratory of Molecular Oncology program.

- **Laboratory of Molecular Virology—**
  George Khoury, M.D.

This laboratory is interested in the normal and abnormal regulation of gene expression. Specific studies employ methods from molecular biology, immunology, virology and cell biology in an attempt to determine in specific cases what signals regulate gene expression. Presently the laboratory is interested in both viral and eukaryotic genetic units. The research efforts are focused on genes which are regulated at the level of transcription and which, in some cases, are responsive to induction by hormones or trans-acting proteins. The laboratory has made a commitment to the study of oncogenes and the mutations which are responsible for the activation of these genes in neoplasia. Studies are being pursued on the histocompatibility antigens in hopes of determining the role of these genes in immune surveillance and tumor immunity.

- **Laboratory of Tumor Virus Biology**
  Peter M. Howley, M.D.

The laboratory engages in several areas of research to determine critical cellular and molecular factors involved in virus-associated transformation. Studies are designed to (1) identify and characterize exogenous viruses associated with the initiation or progression of neoplasia in humans or in animals as models for human neoplasia; (2) elucidate the mechanisms by which viruses associated with naturally occurring carcinomas may induce or initiate neoplasia; (3) characterize and define the biology and molecular biology of viruses associated with naturally occurring carcinomas; and (4) identify and characterize factors involved in viral and cellular gene regulation pertinent to carcinogenesis.

A major research effort of the laboratory is focused on the molecular biology of the papillomaviruses including tran-

scriptional regulation, transformation, plasmid replication, and carcinogenesis. The laboratory has also been involved in the development of the papillomaviruses as mammalian cell cloning vectors and is interested in using these vectors to study regulated gene expression. Studies are designed to determine the gene sequences involved in proper gene regulation and to isolate cellular protein factors required for this regulation.

- **Laboratory of Viral Carcinogenesis—** Stephen O'Brien, Ph.D., Acting

This laboratory is committed to basic research approaches to unravelling the genetic and cellular mechanism of neoplastic transformation in man and in mammalian model systems. Studies are conducted on the specific cellular genes which participate in transformation from several distinct approaches. Endogenous mammalian retroviruses are studied in attempts to understand their role in gene regulation and in neoplasia. Transforming viruses, their included oncogenes and their ancestral cellular homologues are being examined using recombinant DNA technologies and systems for studying their expression during development and during carcinogenesis. Molecular processes of chemical carcinogenesis are studied using gene cloning, cell transfection and cell biology procedures. Somatic cell genetic approaches to neoplastic transformation is an important component of the laboratory as are the cytogenetic consequences of transformation. The laboratory is also studying activities of hormone-like growth factors, and tumor promoters to determine their regulation of transformation sensitivity genes and transforming genes and of the progressive stages of transformation of cells *in vitro* and *in vivo*.

Epidemiology and Biostatistics Program—
Joseph F. Fraumeni, Jr., M.D.
Associate Director

Medical staff fellow positions are available for 2-year assignments in the four branches of the Epidemiology and Biostatistics Program, which provides the focus for epidemiologic and biostatistical research within the Institute. The program conducts epidemiologic investigations into the environmental and host determinants of human cancer; analyzes the natural history of cancer and the efficacy of therapeutic and preventive measures; and designs statistical models for clinical and experimental investigations.

Environmental Epidemiology Branch—
Robert N. Hoover, M.D.

The Environmental Epidemiology Branch conducts a wide range of studies to clarify the risk of cancer among persons exposed to occupational, nutritional, medicinal, radiogenic, infectious or other environmental hazards, and among persons with genetic or immunologic predisposition. Multidisciplinary studies with laboratory scientists are carried out whenever feasible.

Clinical Epidemiology Branch—
Robert W. Miller, M.D.

The Clinical Epidemiology Branch investigates the origins of human cancer by starting from peculiarities of cancer occurrence recognized at the bedside and studied through the disciplines of clinical medicine, epidemiology, and cellular genetics and other laboratory sciences. Current emphasis is given to the clinical delineation of cancer family syndromes and disorders that predispose to cancer, such as neurofibromatosis and certain birth defects, and to studies evaluating the late effects of cancer treatments, including reproductive toxicity. Liaison is maintained with many clinical services throughout the Washington area and beyond, as well as with the NIH Interinstitute Medical Genetics Program. Physicians selecting this Branch need not have specific training in epidemiology or genetics, and may become Board-eligible in medical genetics through the NIH Interinstitute Medical Genetics Program.

Radiation Epidemiology Branch—
John D. Boice, Jr., Sc.D.

This branch conducts studies to identify and quantify the risk of cancer in populations exposed to ionizing radiation, especially at low-dose levels. These include patient populations given diagnostic or therapeutic radiation alone or in combination with cytotoxic drugs and other forms of treatment.

Biostatistics Branch—
William J. Blot, Ph.D.

The Biostatistics Branch uses biometric and mathematical approaches to investigate the distribution, causes and natural history of cancer. New statistical methods are developed for designing and analyzing epidemiologic, clinical, and experimental studies of cancer. Mathematical models are explored to clarify processes of cancer biology and carcinogenesis, and improve methods of quantitative cancer risk assessment.

Division of Cancer Treatment

Bruce A. Chabner, M.D., Director

This Division carries out a broad program of basic and clinical research concerning the treatment of cancer. The major areas of research are radiation therapy, drug therapy, modifiers of tumor growth and differentiation, and surgical approaches to cancer treatment. Treatment programs are multidisciplinary in nature, involving the cooperative efforts of medical, surgical, and radiotherapy staff members.

Cancer Therapy Evaluation Program—
Robert Wittes, M.D.,
Associate Director

One medical staff fellow position is open each year within the Cancer Therapy Evaluation Program. The fellow is assigned to the Investigational Drug Branch for 1 year. Subsequently, a second year program may be developed in conjunction with other branches or laboratories within the Division of Cancer Treatment, or within the Cancer Therapy Evaluation Program by rotating to the Clinical Investigations Branch. It is anticipated that the second-year medical staff fellow will also maintain some responsibility for drug monitoring. Eligibility for a third year within the program is feasible. The duties within the Investigational Drug Branch include developing and coordinating clinical research efforts on specific new antineoplastic drugs developed by the NCI. Special projects in the area of antineoplastic drugs are available. The work within the Clinical Investigations Branch includes developing new research strategies along disease or modality lines, providing overviews of research topics, planning discussion groups and intergroup studies, monitoring research and progress in grant and cooperative agreement programs, and reviewing new research protocols.

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials with investigational chemotherapeutic agents. This includes the incorporation of effective chemotherapeutic combinations in early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities until now considered untreatable. For these purposes, the program has planned and helped organize several study groups designed to test combined modality approaches to specific diseases. The program also supports, through the cooperative agreement mechanism, various clinical cooperative groups made up of university hospitals, cancer centers,

and community hospitals. These cooperative groups share in the design, development, execution, and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research efforts at a national level. Staff members of the program attend meetings of the clinical cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between in-house preclinical and clinical programs and extramural activities.

The program coordinates clinical conferences which are an important mechanism for informing clinical investigators throughout the world on the status of drug trials. The conferences are held to discuss the clinical programs concerned with drug development. The program also maintains a special relationship with the Clinical Oncology Program's branches, the Biological Response Modifiers Program, and the Radiation Research Program. In addition, it is responsible for the development of new areas of clinical research and dissemination of information on clinical trials to investigators in foreign countries, and is responsible for receiving and analyzing information from abroad.

Clinical Investigations Branch—
Michael Friedman, M.D., Chief

The Clinical Investigations Branch monitors and coordinates a broad range of research activities. This includes research support for individual investigator-initiated projects (R01), program project grants (P01), cooperative group agreements (U10), and planning grants (P20). This research spans the spectrum from laboratory research to Phase III clinical trials. Staff responsibilities include critical review and participation in the development of protocols developed by cooperative groups and intergroup studies. Staff members also develop overviews of research progress, formulate strategies for future research directions, and plan discussion groups on selected topics. There is a major emphasis on integration of modalities in the treatment of cancer.

This branch also maintains liaison with international clinical research groups and the Breast Cancer Task Force.

Investigational Drug Branch—
Daniel Hoth, M.D., Chief

This branch monitors and coordinates the drug-oriented trials of the Division. The branch serves as a link between the preclinical and clinical aspects of the drug development part of the Division with special interest in the pharmacologic investigations of new drugs. Interaction with investigators is a vital part of the work of the branch in providing supervision, advice, and retrieving information on therapeutic response and toxicity.

- Regulatory Affairs Branch—
  Dale Shoemaker, Ph.D., Acting Chief

The section provides liaison with the Food and Drug Administration and supervises the preparation of all FDA filings on new drugs. This involves a close working relationship with intramural branches and committees dealing with submission of data to meet regulatory requirements.

This branch also manages the site-visit monitoring program for all clinical trials using NCI-sponsored agents, coordinates all monitoring activities within the clinical cooperative groups, and provides information to all NCI clinical investigators regarding FDA regulations, NCI policies, procedures, and human subjects regulations.

Clinical Oncology Program—
Samuel Broder, M.D.
Associate Director

The Clinical Oncology Program (COP) recruits approximately 18 medical staff fellows each year for a 3-year assignment in medical oncology or a 2-year assign-

ment in surgical oncology. Fellows are recruited for one of the following clinical branches: Medicine, Pediatrics, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-Navy Medical Oncology Branch located at the Naval Hospital Bethesda (NHBETH), Bethesda, Maryland. The program also offers a residency training program in radiotherapy.

The 3-year medical oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine or pediatrics. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients. The staff fellow may sometimes take a full year with a single clinical service, or take two 6-month rotations through the clinical services of the COP. The second and third years consist of clinical and/or laboratory research under the supervision of a member of the senior staff. Medical staff fellows will have the opportunity to select a project from the numerous current studies in the laboratories of the Clinical Oncology Program, the Developmental Therapeutics Program, or the Biological Response Modifiers Program. Opportunities are also available for clinical trial monitoring in the Cancer Therapy Evaluation Program. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second- and third-year medical staff fellows continue to follow patients in the Outpatient Department. Offered throughout the program are lectures, clinical conferences, research seminars, teaching rounds, and joint conferences relevant to the field of clinical oncology and cancer research. Certain clinical conferences are mandatory.

Candidates otherwise qualified who successfully complete the program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology.

For further information, applicants to the medical or pediatric oncology training programs should write to:

Associate Director
Clinical Oncology Program
National Cancer Institute,
Building 10, Room 6B15
Bethesda, MD 20892.

The Surgery Branch offers a 2-year surgical oncology training program. This program consists of a 6-month period on the wards of the Surgery Branch, inpatient and outpatient services, and 1½ years in one of the laboratories of the senior staff in the Surgery Branch. Selected medical staff fellows may remain for a third year to continue their laboratory research. Applicants interested in the Surgery Branch program should write director Steven Rosenberg, M.D., Ph.D., Surgery Branch, Building 10, Room 10N116, National Cancer Institute, Bethesda, MD 20892.

Applicants interested in the radiotherapy residency should write to Eli Glatstein, M.D., Radiation Oncology Branch, Building 10, Room B3B69, National Cancer Institute, Bethesda, MD 20892.

Clinical Pharmacology Branch—
Charles Myers, M.D.

This group conducts laboratory and clinical research activities on problems of drug action and toxicity in man and, as such, plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. The branch does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the other clinical branches. Research training opportunities are available for physicians completing 1 year of clinical training in the Clinical Oncology Program or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include: development of effective therapy for AIDS; mechanisms of adriamycin cytotoxicity; mechanism of action and cellular pharmacology of antimetabolites; pharmacokinetics and metabolism of established and new antineoplastic agents; clinical and experimental applications of cytofluorometry; molecular

genetics of drug resistance; high resolution NMR studies of drug-receptor interaction; development of NMR imaging agents.

Medicine Branch—
Robert C. Young, M.D.

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, breast cancer, ovarian carcinoma, sarcomas, melanoma, AIDS/Kaposi's Sarcoma, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy. The Branch has an active autologous marrow infusion program.

The branch conducts weekly clinical conferences with the departments of radiation oncology, pathology, clinical pathology (hematology), and radiology on current problems and on the staging of lymphomas, Hodgkin's disease, and testicular carcinoma. Research focuses on the general areas of drug resistance and cytogenetics of neoplastic and hemopoietic cells, tumor immunology, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is underway in the field of hormone receptors, and the molecular biology of hormone action. The branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI-Navy Medical Oncology Branch—
John D. Minna, M.D.

The NCI-Navy Medical Oncology Branch is located at the Naval Hospital Bethesda (NHBETH) in Bethesda, Maryland across the street from the NIH Clinical Center. This branch is part of the NCI intramural Clinical Oncology Program and, with the Navy Hematology-Oncology Branch (Steven Veach, M.D., Chief), part of the NHBETH cancer treatment program. The NHBETH is a 450 bed tertiary referral hospital for active duty military, military retired, and military dependents. Patients are referred from around the world with all types of malignant diseases including solid tumors (e.g. lung, breast, gastrointestinal) and hematologic malignancies (Hodgkin's disease, non-Hodgkin's lymphomas, and acute and chronic leukemias). There is a large population of young adults with such malignant diseases as germ cell tumors. The program has a 20-bed inpatient service, and also provides consultation in oncology and hematology to the NHBETH (approximately 40-60 active inpatients at any one time). In addition, civilian patients who are eligible for certain NCI studies can be admitted to the program for care and study. The NCI-Navy Medical Oncology and Navy Hematology-Oncology Branches represent a joint and integrated NCI-Navy effort in cancer patient care, clinical and laboratory investigation, and training in clinical oncology and hematology. More than 2,000 patients are followed by the NCI-Navy Program in a study and primary care setting and each fellow has approximately 150 patients as his or her primary care responsibility. Most fellows spend 6 months at the Clinical Center, NIH, and 6 months at the NHBETH during the clinical year. The clinical research studies involve a wide variety of diseases and represent a collaboration between the intramural Clinical Oncology Program Branches and the NHBETH.

The laboratory investigations of the branch revolve about human tumor cell biology and molecular genetics. These include studies of cell culture, molecular genetics of gene structure, expression and regulation, production of monoclonal antibodies, identification of tumor cell growth factors and pathways of differentiation, and gene transfer techniques. Major efforts involve growing tumors from individual patients and selecting therapy after *in vitro* drug sensitivity testing and the study of oncogenes and peptide hormone genes in human tumors.

The program is designed to include clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals.

Pediatric Oncology Branch—
Philip A. Pizzo, M.D.

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma and neuroblastoma. Children and adolescents are accepted for treatment. Three areas of clinical investigations are stressed: chemotherapy with new or established agents; hematologic support and bone marrow transplantation; and diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 26 inpatient beds and an extensive outpatient department. The branch also has an extremely active teaching program, with 12 weekly clinical and laboratory conferences and seminars. Candidates with prior training in pediatrics may apply to this branch and are eligible for Board certification in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and/or radiotherapeutic means, followed by experimental manipulation to prolong remission. In conjunction with the Medicine Branch, a major area of interest is hematologic reconstitution through autologous bone marrow and stem cell transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient.

In the second and third year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on the cell and molecular biology of pediatric neoplasms (particularly neuroblastoma and sarcomas); clinical pharmacology and pharmacokinetics; tumor immunology; leukocyte physiology and immunoregulation.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—
Eli Glatstein, M.D.

The Radiation Oncology Branch of the National Cancer Institute offers a 3-year training program in radiation oncology. This program is organized in conjunction with the Uniformed Services University of the Health Sciences, through Walter Reed Army Medical Center and the Naval Hospital Bethesda (NHBETH) in Bethesda. The program calls for 18 months at the NCI, 9 months at Walter Reed, and 9 months at the NHBETH.

The program emphasizes all aspects of patient care in radiation therapy with major emphasis on treatment planning and dosimetry. Experimental approaches are emphasized within the National Cancer Institute as part of prospective clinical trials; conventional treatment approaches are emphasized at the military facilities. Work on radiation sensitizing compounds, radioprotecting compounds, intraoperative irradiation, and atypical fractionation schemes will be ongoing at NCI. Areas of investigation include primary breast cancer, carcinoma of the bladder, small cell carcinoma of the lung, lymphoma, Hodgkin's disease, gliomas, mycosis fungoides, soft tissue sarcomas, and pediatric neoplasms. Opportunities for study of a wider spectrum of conditions are available through the military hospitals, with special attention to head and neck cancer and gynecologic neoplasms. The emphasis at all institutions will be on combined

modality approaches and on long-term follow-up to assess success and morbidity.

Preference will be shown to candidates who have completed all or part of training in another oncologic specialty. The director of training for the program is Eli Glatstein, M.D., Radiation Oncology Branch, National Cancer Institute. Interested individuals should contact him.

Surgery Branch—
Steven A. Rosenberg, M.D., Ph.D.

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen, including sarcomas, rectal, breast, esophageal, and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Developmental Therapeutics Program—
Michael R. Boyd, M.D., Ph.D.,
Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, acquisition and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and an extramural program on preclinical development of therapeutic modalities.

Medical Staff Fellows

First-year medical staff fellows in the Clinical Oncology Program are eligible to work in the laboratories of the Developmental Therapeutics Program (DTP) for their second and third years of research training. The following paragraphs describe current projects from which medical staff fellows may elect to participate.

Laboratory of Biological Chemistry—
Richard L. Cysyk, Ph.D.

This laboratory brings together scientists who identify, as targets for drug design, cellular reactions that are critical to tumor cell survival and to the control of cell division and differentiation. Emphasis is placed on targets uncovered by recent advances in cell biology. Compounds are designed to interfere with these targets and are evaluated for biochemical and antitumor effectiveness. Pharmacologic information—plasma levels, tissue levels, mechanism of action, transport, and metabolism—is used for experimental chemotherapy and for preclinical evaluation of the agent. An important aspect of the selective toxicity of an agent is the effect of endogenous factors present *in vivo* that can modify

the cytotoxic properties of an agent and thereby influence differential toxicity. This laboratory identifies and quantitates such endogenous factors, when possible, and devises methods to manipulate them to enhance the chemotherapeutic effectiveness of cytotoxic compounds.

Laboratory of Pharmacology and Experimental Therapeutics—
David G. Johns, M.D., Ph.D.

The Laboratory of Pharmacology and Experimental Therapeutics is made up of three Sections: Medicinal Chemistry, Molecular Toxicology and Biochemical Pharmacology. The Laboratory conducts an integrated program for the rational discovery of antitumor agents, implements basic research on mechanisms of antitumor drug action and drug toxicity, incorporates knowledge of biochemical/molecular mechanisms into a drug synthesis program aimed at optimizing drug efficacy through enhancement of antitumor activity/selectivity and/or minimization of toxicity, and develops strategies for improving the clinical utility of new or existing anticancer drugs by overcoming tumor resistance and/or by protection of normal tissues against toxicity. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites, e.g., nucleic acids, nuclear proteins, microtubular protein, and enzyme systems. Analytical methodology for *in vivo* studies with new agents is developed and, where warranted, biological studies with these agents are extended to the preclinical and Phase I stages. At the present time, three agents synthesized and developed within LPET are Phase I/II clinical trials, while a fourth agent is scheduled for clinical trial within the next year. Other agents are under active study. A wide range of methodologies is currently in use, including soft agar cloning and other tissue culture techniques, instrumental analysis, with emphasis on mass spectrometry, electron microscopy, HPLC, affinity chromatography, DNA and RNA isolation and characterization, hybridization, autoradiography, pharmacokinetic analysis and enzyme purification.

Laboratory of Molecular Pharmacology—
Kurt W. Kohn, M.D., Ph.D.

Mechanisms of action of anticancer agents are studied in culture and subcellular systems with particular attention to effects involving DNA and nuclear proteins. These investigations focus on the relation between drug-induced macromolecular damage (and its repair) and cell survival. Secondly, drugs are used as probes of the structure and function of DNA and chromatin. Experimental approaches include cell culture, DNA macromolecular damage measurements, DNA sequence analysis, and nuclear protein fractionation techniques. A major area of current interest is the effects of anti-cancer drugs on topoisomerase enzymes.

Laboratory of Tumor Cell Biology
Robert C. Gallo, M.D.

The objectives of the Laboratory of Tumor Cell Biology are to develop, implement, and analyze data obtained from studies of cellular proliferation, cell differentiation, and biochemical growth characteristics of normal and malignant mammalian cells both *in vivo* and *in vitro*. Particular attention is given to hematopoietic cells, their normal behavior and especially changes seen during leukemogenesis. The laboratory focus is on the studies on human leukemias, lymphomas, acquired immune deficiency syndrome (AIDS), and AIDS-related complex (ARC). It is anticipated that an enhanced understanding of cell regulatory mechanisms will permit the optimal use of anti-tumor agents in the therapy of cancer, AIDS and the development of new approaches. Many studies are directed to the origin of these diseases, especially the role of certain viruses and certain cell genes called "*onc*" genes.

The Laboratory of Tumor Cell Biology is concerned with several biological and biochemical problems: (1) Studies on the cellular and molecular origin and pathogenesis of human leukemia and AIDS. Biochemical control mechanisms involved in cell differentiation and

neoplastic transformation are examined. Tumor viruses of animals are used both as tools (to define and isolate genes and gene products important for growth in man) as well as for help in understanding mechanisms of naturally occurring animal leukemias. Also, studies designed to determine the involvement of human T-cell leukemia virus (HTLV) in T-cell malignancies and AIDS are intensively investigated. (2) Studies on the biochemical events preceding mitosis appear essential to the control of proliferation. Information derived from such studies may lead to a better understanding of the control of cell proliferation and development of more effective inhibitors of neoplastic cell growth. (3) Attempts to develop new approaches to cancer chemotherapy and to control AIDS using information gained from basic cellular studies. (4) Studies on the development of biochemical and immunological markers for malignant cells. Biochemical and immunological studies are also conducted in individuals with disorders associated with an increased incidence of neoplasia and AIDS or AIDS-related complex (ARC). (5) Controls regulating cellular growth and differentiation, and the process of malignant transformation in hematopoietic cells. (6) Growth factors (and their receptors) that control the growth and differentiation of blood cells have been isolated and are under intensive study, e.g., T-cell growth factor (TCGF), CSF, and related hematopoietic growth effecting molecules. (7) Human T-lymphotropic virus (HTLV) has been isolated from patients with T-cell malignancies and AIDS and AIDS-related complex (ARC). Biochemical, biological and molecular biological studies to characterize HTLV belonging to different subgroups (I, II, III), and seroepidemiological studies to determine the extent of HTLV infection in patients with T-cell malignancies; AIDS and AIDS-related complex (ARC) around the world are in progress.

National Eye Institute

Carl Kupfer, M.D.,
Director
Carl Kupfer, M.D.,
Acting Clinical Director
Jin Kinoshita, Ph.D.
Scientific Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three medical staff fellows from those candidates who have completed an accredited 3-year ophthalmology program. Fellows spend time in both clinical and laboratory research including patient care activities.

In selection of medical staff fellows, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Office of Biometry and Epidemiology— Daniel Seigel, Ph.D.

The Biometry and Epidemiology Program conducts studies in the areas of clinical trials, natural history, and epidemiology.

The Clinical Trials Branch is currently responsible for three national multiclinic trials involving vitrectomy, drugs, and photocoagulation, as treatments to prevent disease progression in patients with diabetic retinopathy. These studies include hundreds or thousands of patients, and combine the skills of opthalmologists and biostatisticians. Data

generated in these studies not only provide a base for treatment strategies, but permit investigation of factors other than treatment related to disease progression.

The Epidemiology Branch conducts studies of the prevalence and incidence of diseases of the eye in the general population, and of personal, environmental, genetic, and biologic factors in the population that may be related. Data from these studies are used to generate and evaluate hypotheses about the causes of such diseases. Data from the Framingham Eye Study and the Health and Nutrition Examination Survey are being analyzed to explicate the risk factors for changes in the lens and retina. A major national case-control study to investigate factors related to the development of several eye diseases will soon be under way, as well as a re-survey of the Framingham population for factors related to the incidence and natural history of cataract and age-related maculopathy.

Laboratory of Vision Research—Gerald Chader, Ph.D.

This laboratory conducts research of normal and pathological processes in ocular tissues with the primary focus on lens and retinal tissues.

Lens and Cataract—This unit, headed by Dr. J. H. Kinoshita, investigates the underlying reasons for transparency of the normal lens and for the development of cataracts. Lens proteins are being investigated in regard to their relationship to cataract development. The genetic influence on synthesis of lens proteins and on cataract development in the neonate is being intensively studied. Oxidative stress is thought to lead to cataract development and is being studied as well. The role of the enzyme aldose reductase in the cataract process is also under examination. It is thought that this enzyme may play a critical role in ocular complications of diabetes and is actively being studied.

Experimental Immunology—Research directed by Dr. Igal Gery centers on the study of inflammatory diseases of the eye. Dr. Gery is studying models for human uveitis and the pathogenic processes of experimental autoimmune uveitis (EAU). EAU can be experimentally induced in animals by immunization with purified retinal proteins, notably, the S-antigen and the Interphotoreceptor Retinoid-Binding Protein (IRBP). It has been found that the diseases induced by the two retinal proteins are generally similar but also demonstrate some important differences. The pineal gland of the brain and its role in inflammatory diseases is also being studied. Study of the immunological relationship between the retina and pineal is in progress.

Cell Biology—Dr. Paul O'Brien and other section members are interested in the broad mechanisms of photoreceptor function. The normal and abnormal synthesis of rhodopsin is being studied. Rhodopsin is a glycoprotein, and thus the carbohydrate moiety of the protein is being examined as to its possible role in the function of this visual pigment. It has also been found that the protein is acylated; this may be another mechanism by which the synthesis and/or function of the protein can be regulated. The abnormal synthesis of photoreceptor cell proteins is being studied in several animal mutants of inherited retinal degeneration. In one of these, it has been found that photoreceptor outer segment disc assembly is aberrant, offering an opportunity for determining factors that control the normal assembly of discs as well as a possible model for human retinitis pigmentosa.

Retinal Metabolism—Research directed by Dr. Gerald Chader centers on elucidating important new processes of retinal function and dysfunction with reference to hereditary diseases of the retina such as retinitis pigmentosa (RP) and retinoblastoma. Two scientific areas are emphasized. The first involves the putative role of cyclic nucleotides, especially cyclic GMP, in the normal visual process and in animal mutants of inherited retinal degeneration. Cyclic GMP may function as a phototransducer in the normal visual process and a pathologically induced increase in cyclic GMP may lead to photoreceptor cell degeneration in RP-like diseases. The second area of interest concerns the general role of retinoids in

retinal function. A new protein, the Interphotoreceptor Retinoid-Binding Protein (IRBP) has been discovered which may function as a transport vehicle for vitamin A between retina and pigment epithelium. The cell and molecular biologies of this protein are under investigation.

Laboratory of Sensorimotor Research— Robert Wurtz, Ph.D.

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visualmotor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movements are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and subcortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanism by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain-damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the online laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

Laboratory of Molecular and Developmental Biology— Joram Piatigorsky, Ph.D.

This laboratory conducts basic research on cellular and molecular biology. Emphasis is given to molecular and developmental genetics. The research is designed to elucidate both normal and disease processes. Particular attention is given to hereditary diseases which can be studied at the gene level. Much (but not all) of the work uses eye tissue as models for general problems concerning cellular differentiation and gene expression. Normal and pathogenic visual processes are also being related to the structure and function of genes. Phospholipid metabolism—particularly at the cell membrane—is also under investigation in order to advance our knowledge of cellular differentiation and differential gene expression.

Laboratory of Ophthalmic Pathology— Toichiro Kuwabara, M.D.

This laboratory conducts basic and applied research in structural and functional changes in the eye caused by disease and congenital abnormalities. The laboratory participates in the diagnosis of eye problems by performing pathological studies of diseased tissues removed from

patients. The laboratory will conduct research utilizing the modern techniques available to uncover the cause and nature of eye diseases and will provide training opportunities in ophthalmic pathology.

The laboratory is actively engaged in research on uveitis, diabetic retinopathy, corneal dystrophies, and corneal wound healing. Considerable emphasis is placed on the application of DNA technology to the study of hereditary diseases that affect the eye such as gyrate atrophy, retinoblastoma, and cataracts.

Clinical Branch—
Robert B. Nussenblatt, M.D.

The branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment.

- Cataract Section—
  Jin Kinoshita, Ph.D.

Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

- Section on Neuro-ophthalmology
  Carl Kupfer, M.D.

Patients from the ophthalmic and neurologic service are being studied using advanced methods for computer analysis of eye movements, pupillometry, videotape recording, and event-related potentials. The main emphasis of these studies is on cerebellar disorders that affect ocular movements, parietal mechanisms of attention, and abnormalities of pupil functioning.

- Section on Ophthalmic Genetics and Pediatric Ophthalmology—
  Muriel I. Kaiser, M.D.

These include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogenesis of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism, and abnormalities of the anterior chamber angle associated with glaucoma. There is an active participation in the Interinstitute Genetics Program and a variety of genetic conditions with ophthalmic manifestations are seen.

Bi-monthly genetic counseling is given to students at the Maryland School for the Blind.

- Section on Retinal and Ocular Connective Tissue Diseases—
  Robert B. Nussenblatt, M.D.
  Monique Roy, M.D.

Retinal deteriorations—Clinical, biochemical, cell biological, and metabolic investigations are being conducted to define underlying mechanisms in diseases such as senile macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest. The retinal pigment epithelium, its normal function, pathophysiology, and interrelationships are of special interest. Family studies of macular and retinal degenerations are emphasized. A controlled, double-masked clinical trial to test the value of antioxydents in preventing visual loss from senile macular degeneration is underway.

Vascular diseases—Clinical investigations are being conducted in the treatment and underlying mechanisms of diabetic retinopathy.

- Section on Ocular Immunology—
  Robert B. Nussenblatt, M.D.

Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular auto-

immunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e., toxoplasmosis, pars planitis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of patients with ocular inflammatory disease to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell activity, and macrophage responsiveness. Patients are, in addition, being sought for a controlled double masked study in the therapy of endogenous uveitis.

National Heart, Lung, and Blood Institute

Claude Lenfant, M.D.
Director
Jack Orloff, M.D.,
Director of Intramural Research
Harry R. Keiser, M.D.,
Clinical Director

Candidates for research and clinical positions as medical staff fellows have only one interview in this Institute. Medical staff fellows are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the fellow and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each fellow will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the fellow's training and experience as well as desires.

Each medical staff fellow will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as medical staff fellow are for a minimum of 2 years with a third optional year. In the past, most fellows have elected to remain for 3 full years and have been accorded this privilege.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years of residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical fellowship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory during the previous 2 years of training and is satisfactory here.

Medical staff fellows will be responsible, under the guidance of investigators on the NHLBI staff, for the primary

medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, hematology, and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The fellow devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the second or the optional third year for fellows who have chosen nonclinical laboratories.

Medical Staff Fellows in Surgery

The Surgery Branch appoints four to five fellows yearly for a 2-year interval. The fellowship is designed to provide an intensive 9-month interval of clinical cardiac surgery and cardiology experience with extensive responsibilities for surgical care. Six to eight weeks are spent as a Chief Fellow responsible for all clinical activities; 15 months are devoted to clinical and/or laboratory research under the supervision of preceptor of the fellows' selection. The formal educational program includes weekly branch conferences and lectures in clinical pharmacology, pathophysiology and basic science. Additionally, weekly Surgery Branch and joint cardiac catheterization conferences are scheduled throughout the year as are monthly mortality and morbidity conferences. The laboratory opportunities are extensive and include large animal surgery, studies in cardiac physiology, biochemistry and pathology. Prosthetic heart valves and other device development and evaluation are major programs as are novel revascularization and laser projects.

The fellowship is restricted to those with excellent academic and clinical recommendations who have a full-time academic career as a goal. Candidates must have completed a minimum of 2 core years in an approved surgical residency training program, although 3 years of prior training are preferred. Interested candidates are encouraged to write to Richard E. Clark, M.D., Chief, Surgery Branch, NHLBI, Bldg. 10, Room 2N242, National Institutes of Health, Bethesda, MD 20892.

Appointments in Laboratory Research

These appointments are designed to give highly qualified physicians an opportunity to do either clinical or basic research in any area of the Institute under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NHLBI programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Staff Appointments

Laboratories within NHLBI sometimes have openings for medical staff fellows appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory.

Joint Endocrinology Training Program

Medical staff fellows from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to quality fellows for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the fellow will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the fellow's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two NHLBI fellows to enter this program in any one year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate School of the Foundation for Advanced Education in the Sciences, Inc. Medical staff fellows are expected to take advantage of this academic work. (See part 4, page 143.)

Clinical Research Branches

Cardiology Branch—
Stephen E. Epstein, M.D.

The Cardiology Branch is involved in a broad range of clinical and basic research efforts. Studies are being carried out in both the Catheterization and Animal Physiology Laboratories oriented towards elucidating of the clinical significance and mechanisms responsible for myocardial ischemia caused by disease of the small coronary arteries. Another major effort is directed towards the developing approaches to revascularize the heart, including the promotion of angiogenesis. Investigations are also being carried out in the hypertrophic and dilated cardiomyopathies: the underlying thrust is to develop more effective therapeutic approaches to these entities as well as to determine pathophysiologic mechanisms. A major effort is also being taken to determine the clinical implications of abnormalities of diastolic function. These studies are being carried out largely in the Nuclear Medicine and Cardiac Catheterization Laboratories. Other interests are oriented towards the diagnosis of acquired and congenital heart disease, the evaluation of operative and nonoperative forms of treatment of these conditions, and a study of the mechanisms responsible for the hemodynamic changes produced by various cardioactive agents, with particular emphasis on calcium antagonists.

Clinical Hematology Branch—
Arthur W. Nienhuis, M.D.

The research activities in this branch, while diverse, are generally focused on the problems of red cell production, hemoglobin synthesis, and hemoglobin function. Syndromes of bone marrow

failure, chiefly aplastic anemia, are investigated in the laboratory and with experimental therapeutic protocols. Stem cell function, cell-cell interactions, lymphocyte populations and their function, and the production of various hematopoietic factors are assayed by *in vitro* techniques to define the pathogenesis of bone marrow hypofunction. Experimental treatments under study include immunosuppressive and antiviral agents. Regulation of the several globin genes is being studied in the context of developmental switches in the hemoglobin phenotype in man and other species. Furthermore, the study of gene expression in patients with thalassemia is directed toward definition of molecular defects that result in deficient hemoglobin synthesis in these syndromes. Various strategies are being devised and tested with the long term goal of introducing functional genes into the erythroid cells of such patients. Treatment protocols include the evaluation of various cytotoxic drugs for their potential to stimulate fetal hemoglobin production in patients with thalassemia and sickle cell anemia.

Hypertension-Endocrine Branch—
Harry R. Keiser, M.D.

This branch represents a merger of the former Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension; activities are wide-ranging, as indicated by the description of section activities.

- Section on Experimental Therapeutics—
  Harry R. Keiser, M.D.

A wide spectrum of research opportunities is offered, ranging from basic biochemistry, physiology and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, renin-angiotensin-aldosterone system, prostaglandins and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin, histamine, and peptides.

There is also a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. Molecular biological, biochemical, and pharmacological techniques are used. Again the role of these systems in disease states particularly hypertension, is of prime interest.

- Section on Biochemical Pharmacology—
  Walter M. Lovenberg, Ph.D.

This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. Molecular biological, biochemical, and pharmacological techniques are used. The role of these systems in disease states, particularly hypertension, is of prime interest, and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch—
H. Bryan Brewer, M.D.

The research activities of this branch are directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Biochemical studies take several approaches including protein chemistry, immunology, tissue culture, molecular biology, and enzymology. Clinical research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemia and on kinetic analysis of the metabolic defects in patients with these diseases. Activities are integrated in such a way that, if medical staff fellows wish, they may participate in collaborative research involving several different areas.

Pathology Branch—
William C. Roberts, M.D.

This branch is concerned with the study of morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include

transmission and scanning electron microscopy.

Pulmonary Branch—
Ronald G. Crystal, M.D.

Research in this branch is designed to investigate the structure and function of the lung in health and disease through cellular and biochemical methods. Both laboratory and clinical investigations are conducted. Techniques of protein chemistry, molecular biology, tissue culture, and immunology are used. Emphasis is placed on the regulation of the inflammatory and immune processes in the normal and diseased lung. Clinical research is directed toward correlating physiologic, biochemical, immunologic, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, hypersensitivity lung disease, and other lung disorders with an immunologic basis.

Surgery Branch—
Richard E. Clark, M.D.

The clinical research programs are designed to span prospective longitudinal studies of surgical therapies to developing unique prosthesis and support systems for the critically ill cardiac patient. Major areas of interest include, but are not limited to, development of improved myocardial preservation techniques and definition of relevant end points, studies in bioprosthetic and new mechanical valvular prostheses, metabolic studies of pulsatile perfusion and membrane oxygenation, intrinsic coronary vasomotor tone alterations as a function of cardiac surgery. Other studies involve capillary permeability in pulmonary hypertension, development of small diameter vasular prostheses and new immunologic approaches to heart transplantation. Approaches to these areas are multidisciplinary and encourage interaction with biochemistry, biophysics, materials science, pharmacology, ultrastructural pathology, platelet pathophysiology and immunology. Didactic educational sessions include advanced clinical cardiac pharmacology, research conferences, statistical methods, Fellows clinical interdepartmental conference and a guest lecturer program.

Basic Research Laboratories

Laboratory of Biochemical Genetics—
Marshall Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry are studied in this section, particularly those that pertain to the development of the nervous system. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Many monoclonal antibodies have been generated and are being used as probes for synaptic and other antigens. Cultured cells are used in many studies. Research also is being conducted on cyclic nucleotides, ion channels and cell recognition.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control in *Escherichia coli*. One area of interest concerns the control of the synthesis and metabolism of cyclic AMP in bacterial cells. Current information suggests that cyclic AMP concentrations in *E. coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells. The laboratory is using biochemical and recombinant DNA approaches to study the regulation of expression of the gene for adenylate cyclase as well as the factors that regulate the enzyme activity. Another focus of attention is the *E. coli* cyclic AMP receptor protein. Analyses of structure, function and repression mechanisms involving this protein are under way.

Laboratory of Biochemistry—
Earl R. Stadtman, Ph.D.

- Section on Enzymes—
  Earl R. Stadtman, Ph.D.

Studies of this group are concerned with the elucidation of various mechanisms of metabolic regulation, specifically,

studies on the regulation of enzyme activities by allosteric interactions, by enzyme catalyzed covalent modification (phosphorylation, nucleotidylation, etc.) of interconvertible enzymes, and on the regulation of enzyme levels by changes in the rates of protein degradation mediated by mixed-function oxidase catalyzed inactivation of enzymes. These studies involve the isolation and characterization of key regulatory enzymes and of the enzymes which catalyze their covalent modification, oxidative inactivation, and proteolytic degradation.

- Section on Intermediary Metabolism and Bioenergetics—
  Thressa C. Stadtman, Ph.D.

This section is concerned primarily with investigations on the mechanisms of anaerobic metabolism of one-carbon compounds and amino acids and phosphorylation reactions coupled to the electron transfer processes. Emphasis is on the roles of various coenzymes (*e.g.*, vitamin B_{12} coenzyme, CoA, deazaflavins, quinones) and electron transfer proteins such as selenoproteins, molybdo-iron sulfur proteins and flavoproteins. The occurrence and roles of selenium in enzymes and amino acid transfer nucleic acids are being investigated currently.

- Section on Protein Chemistry—
  Ann Ginsburg, Ph.D.

Studies on protein structure in this laboratory are directed toward understanding the roles of ligand binding and of protein-protein interactions in enzyme catalysis and regulation.

- Section on Metabolic Regulation—
  P. Boon Chock, Ph.D.

This section conducts biophysical studies on various enzymes and proteins with emphasis on the mechanisms of enzyme action and its regulation. Currently, we are investigating the roles of covalent modification in metabolic regulation of enzymes. This involves the study of the glutamine synthetase cascade and the phosphorylation/dephosphorylation ca cade. In addition, we are studying the mechanism for the activation of cyclic nucleotide phosphodiesterase and calcineurin by calmodulin, enzyme-monoclonal antibody interaction, and glutamine synthetase catalysis.

Laboratory of Cell Biology—
Edward D. Korn, Ph.D.

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

- Section on Cellular Biochemistry and Ultrastructure—
  Edward D. Korn, Ph.D.

This section studies the biochemistry of actomyosin-dependent cell motility, the process involved in such diverse phenomena as ameboid movement, phagocytosis, cytokinesis and determination of cell shape. Research includes the mechanism of actin polymerization including the role of ATP hydrolysis in the polymerization process and the regulation of actin polymerization process and the regulation of actin polymerization and actin filament organization through the interaction of monomeric and polymeric actin with other cell proteins. A second major activity is the study of the mechanism of the regulation of myosin filament formation and actomysin ATPase activity by phosphorylation of heavy and light chains of myosins of non-muscle origin. Approaches to these problems include protein physical chemistry, kinetics, electron microscopy and molecular biology.

- Section on Cellular Physiology—
  Evan Eisenberg, M.D., Ph.D.

This section studies the basic molecular events which underly cardiac and skeletal muscle contraction as well as many forms of cell motility. The section also investigates how the free energy of ATP hydrolysis is transformed into mechanical work and how this energy transduction process is regulated by control proteins such as troponin-tropomyosin. By collaborating with other laboratories at NIH investigating the physiology of muscle contraction, we try to relate the biochemical behavior observed with purified proteins to the physiological behavior of single muscle fibers. The emphasis is on understanding how the organization of

proteins into supramolecular systems enables their biochemical properties to be manifested in physiologically useful ways.

- Section on Membrane Enzymology—Richard W. Hendler, Ph.D.

This section studies enzyme systems that require organization on, or interaction with, membranes in order to ensure their proper functioning. The structure of mammalian electron transport chain and the mechanism of energy transduction are being investigated.

- Section on Organelle Biochemistry—Martin Flavin, M.D., Ph.D.

This section is currently concerned with posttranslational modifications of microtubule protein, and their possible effects on microtubule structure and function in brain.

Laboratory of Cellular Metabolism—Martha Vaughan, M.D.

- Section on Metabolic Regulation—Martha Vaughan, M.D.
- Section on Biochemical Physiology—Vincent C. Manganiello, M.D., Ph.D.
- Section on Molecular Mechanisms—Joel Moss, M.D., Ph.D.

Using techniques of molecular genetics, biochemistry and cell biology, this laboratory conducts research directed toward understanding the regulation of cyclic nucleotide synthesis and degradation. Cyclic AMP synthesis by the membrane-associated adenylate cyclase complex is controlled by stimulatory and inhibitory agaonists (e.g., hormones, drugs) acting through cell-surface receptors. Signals generated by receptor-agonist interation are transmitted to the cyclase catalytic unit via GTP-binding coupling proteins, which are targets for covalent modification (ADP-ribosylation) catalyzed by bacterial toxins (e.g., cholera toxin, pertussis toxin) that activate the cyclase. Areas of current interest include: (1) molecular biology; isolation of cDNAs and genes for the regulatory components of adenylate cyclase; analysis of mRNA content and structure in differentiating systems: (2) membrane biochemistry: molecular mechanisms for the interaction of adenylate cyclase components (e.g., studies with site-specific monoclonal antibodies, reconstitution of purified proteins) and effects of toxin-catalyzed ADP-ribosylation on the interaction of coupling proteins with receptors and the cyclase catalytic unit; (3) cell biology: effects of hormones and toxins on cyclic nucleotide content of cultured cells; and (4) enzymology: identification of ADP-ribosyltransferases and their substrates in animal cells, effects of ADP-ribosylation on enzyme function, regulatory properties of the phosphodiesterases that degrade cyclic nucleotides, and mechanisms by which calmodulin modifies the activities of phosphodiesterase and other proteins with which it interacts.

Laboratory of Chemical Pharmacology—James R. Gillette, Ph.D., Chief
Michael A. Beaven, Ph.D.
Deputy Chief

- Section on Drug-Enzyme Interaction—James R. Gillette, Ph.D.

The interests of this section center on various aspects of drug disposition including pharmacokinetics and the relationship between drug metabolism and drug toxicity. Its main objectives have been understanding the mechanisms of drug metabolism by enzyme systems in liver microsomes, and pharmacokinetic factors that govern the conversion of inert substances to alkylating agents and other biologically active metabolites.

- Section on Drug-Tissue Interaction—Gopal Krishna, Ph.D.

This section studies the initial events occurring in cells as the result of a variety of drug cell interactions, including the role of cyclic nucleotides and calcium as mediators of hormone actions, cell function and disease. It also investigates the role of calcium and ATP in cell damage induced by drugs, such as adriamycin and daunomycin, in cardiac myocytes in culture. Various mechanisms in drug-induced peroxisomal proliferation as well as drug-induced liver injury are also being actively investigated.

- Section on Cellular Pharmacology Michael A. Beaven, Ph.D.

This section studies mechanisms of release and action of inflammatory mediators, especially in isolated cell systems. Current work includes studies of the role

of Ca^{++} and inositol phospholipids in the mechanism of mast cell degranulation in freshly isolated and cultured mast cells and basophils, the properties and cellular location of enzymes involved in histamine synthesis and degradation, the role of vascular endothelial cells in the generation and destruction of inflammatory mediators, and the effect of drugs on mediator release.

- Section on Pharmacological Chemistry—
  Lance R. Pohl, Pharm. D., Ph.D.

This Section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identication of active substances formed in the body, the biochemical basis of their pharmacologic and toxicologic actions, and the characterization and regulation of the enzymes that either produce or metabolize these agents. This Section is particularly interested in the mechanism of drug-induced autoimmune diseases. In addition, it is involved in the study of the mechanisms and regulation of the turnover of cytochromes P-450 in the liver, adrenals, testes, and ovaries.

Laboratory of Chemistry—
Henry M. Fales, Ph.D.

This laboratory investigates the physical and chemical properties of molecules with a view to elucidating their biochemical functions. Specialties are nuclear magnetic resonance, mass spectrometry, x-ray crystallography, chromatography, and laboratory computer. A special concern is the development of new techniques and their application to problems of current interest. Extensive collaborations are carried out with chemists, physicists, clinicians, biologists and computer specialists.

- Section on Chemical Structure—
  Henry M. Fales, Ph.D.

The nuclear magnetic resonance group develops methods for carrying out studies of biologically important systems both *in vitro* and *in vivo* including cellular systems. Such studies involve conformation and activity of intermediate molecular weight peptides and small proteins, identification and characterization of metabolites *in vivo,* investigations of metabolic pathways and determinations of the related rates.

Mass spectrometric studies include gas liquid chromatographic analysis of trace amino acids, drug metabolites, urine components in diseased states, and insect and plant toxins. New methods are developed for applying the method to high molecular weight involatile substances and for elucidating structures of ions by controlling fragmentation.

The crystallographic work of the section consists of determining the structure at atomic resolution over the whole range of molecular weights at which such techniques are feasible. Results are interpreted in terms of physiological action and chemical behavior. Interpretation can include molecular mechanics and molecular orbital techniques. Recent examples include colchinoids, cyclic peptides related to actinomycin, metal complexes in cancer therapy and carcinogens. The section is also interested in the development of computer programs for use in all areas of its research and in applications of the personal computer in the laboratory.

- Section on Structural Nuclear Magnetic Resonance—Robert H. Highet, Ph.D.

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. These include the development of multidimensional pulse Fourier transform methods. Typical studies may include investigation of solution conformations, structures and equilibria of tautomers, and the identification of primary and secondary metabolites of animal and plant origin. The studies expand and utilize the structural dependence of NMR parameters.

Laboratory of Kidney and Electrolyte Metabolism—
Maurice B. Burg, M.D.

- Section on Electrolyte Transport—
  Jack Orloff, M.D.
- Section on Renal Mechanisms—
  Maurice B. Burg, M.D.
- Section on Membrane Metabolism—
  Joseph S. Handler, M.D.

This laboratory conducts research on the mechanism and regulation, hormonal and otherwise, of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, and epithelial cell cultures. Electrophysiology, quantitative microscopy, nuclear magnetic resonance, and intermediary metabolism as related to transport are emphasized.

Laboratory on Molecular Cardiology— Robert S. Adelstein, M.D.

The regulation and function of the contractile proteins in muscle and nonmuscle cells are being studied. The role of calcium, calmodulin and phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include the mechanism by which phosphorylation alters controctile activity in smooth muscle and nonmuscle cells, regulation of contractile protein expression in cultured smooth muscle cells, and cloning the genes for selected contractile proteins. The role these proteins and their genes play in cellular development, differentiation, and tumorigenicity is of current interest.

Laboratory of Molecular Hematology— W. French Anderson, M.D.

This laboratory studies the mechanism and regulation of mammalian gene expression, using immunodeficiency diseases and hemoglobin biosynthesis as primary models. The major objective is to develop the understanding and techniques necessary to carry out gene therapy for human genetic diseases. Major areas of research include: gene cloning and gene transfer, retroviral vector development, isolation and characterization of *trans* factors involved in gene expression.

Laboratory of Technical Development Robert L. Bowman, M.D.

This laboratory conducts research on instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

- Section on Biophysical Instrumentation—Robert L. Berger, Ph.D.

This section uses new physical, chemical, and computer science technology to develop new instruments and methods for the study of the mechanism of action of biological macromolecules particularly the chemical equilibria and kinetics as these molecules react with ligands. Current work involves the development of highly sensitive batch, flow, titration and scanning, microcalorimeters, as well as a new family of fast flow devices for quench, stopped flow, and accelerated flow studies.

- Section on Pulmonary and Cardiac Assist Devices— Theodor Kolobow, M.D.

This section conducts a program to develop and apply devices for extracorporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators, blood pumps, and control systems.

National Institute on Aging

T. Franklin Williams, M.D.
Director
Richard C. Greulich, Ph.D.
Scientific Director
Reubin Andres, M.D.
Clinical Director

Medical Staff Fellows

The Intramural Research Program of the National Institute on Aging (NIA) is comprised of eight Laboratories. Seven of these are located in Baltimore, Maryland at the Gerontology Research Center (GRC) on the campus of the Francis Scott Key Medical Center, a Johns Hopkins Medical Institution. The remaining one, the Laboratory of Neurosciences, is located at the NIH in Bethesda.

At both locales, two year programs in both basic and clinical research are

available with possible extensions up to three to seven years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a medical subspecialty board. Preference is given to candidates who intend to pursue careers in investigative and academic medicine.

In addition to these fellowship opportunities, combined combined clinical and research are also available with the Johns Hopkins University and the Francis Scott Key Medical Center. For example, one or more years of clinical geriatrics or cardiology training at the JHU-FSK may be followed by two or more years at the GRC, NIA. This program requires dual acceptances by both institutions (JHU-FSK and GRC). The usual pattern is one year of clinical training followed by two years of research. Flexibility is possible, however, including the initiation of research activities during the clinical year and continuation of clinical activities during the research years. The research years may be spent in any of the seven GRC laboratories listed below in accord with the aptitudes, experience and career goals of the individual fellows.

Medical staff fellows are encouraged to participate in seminars conducted by the NIA Center's staff who present a comprehensive view of research in aging and related topics. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical investigation is the Baltimore Longitudinal Study of Aging. The subjects are volunteers who range in age from the late teens years into the 90s and reside in the community, they return for extensive studies every 2 years, spending 2½ days as inpatients each visit, and are enrolled for their entire lives. The study of men is now of 28 years' duration; the study on women began in 1978. There are now 1000 active participants.

In addition to these Longitudinal Studies of normative aging and of mechanisms underlying age changes, studies of age-disease interactions are investigated at the General Clinical Research Center; joint out-patient and in-patient studies may be conducted.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Extensive computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

Prospective candidates wishing further information should write to either Richard C. Greulich, Ph.D., Scientific Director, or Reubin Andres, M.D., Clinical Director, NIA Gerontology Research Center, 4940 Eastern Avenue, Baltimore, MD 21224. Prospective candidates wishing specific information about the Laboratory of Neurosciences should write to Robert Friedland, M.D., Deputy Clinical Director, NIA, Building 10, Room 10N314, Bethesda, MD 20892 or to Stanley I. Rapoport, M.D., Chief, Laboratory of Neurosciences, NIA, Building 10, Room 6C103, Bethesda, MD 20892.

Research Branches and Laboratories

Laboratory of Clinical Physiology—Reubin Andres, M.D.

This laboratory is concerned primarily with studies on physiologic changes occuring over the entire adult lifespan. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- Endocrinology Section—Robert I. Gregerman, M.D.

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those

related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and neuroendocrinology. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on tissues from a variety of organs; cell culture techniques are used with hormone-sensitive and producing cells, especially of adipose and pituitary origin.

- Metabolism Section—
  Reubin Andres, M.D.

This section emphasizes clinical research on such metabolic variables as: glucose-insulin homeostatic mechanisms and diabetes mellitus; serum lipids, the hyperlipidemias, and adipose tissue metabolism; obesity, patterns of fat distribution, and body composition; acute and sustained effects of physical activity; dietary and nutritional evaluation; the interactive effects of these variables on rates of aging, on disease development, and on longevity. There is close collaboration of this Section with the Research Program on the Geriatric Division at FSK under Dr. Andrew Goldberg.

- Clinical Immunology Section—
  William H. Adler, M.D.

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigations of the mechanisms of these deficiencies in humans and experimental animals.

- Applied Physiology Section—
  Jordan D. Tobin, M.D.

Investigators in this unit study age changes in human beings in specific systems including renal, bone, and musculoskeletal. They investigate interrelationships between age effects in different organ systems and in overall physiological changes in individuals. Efforts are made to differentiate between pathological disease changes and those secondary to pure age effects. Others in this section develop and adapt computer techniques for kinetic modeling of physiological systems for the analysis of longitudinal data.

Laboratory of Behavioral Sciences—
Bernard T. Engel, Ph.D.

This Laboratory conducts clinical research on the application of behavioral methods and principles in the assessment, control, and treatment of age-related medical disorders.

- Behavioral Medicine Section—
  Bernard T. Engel, Ph.D. (Acting)

Scientists conduct laboratory and field studies of the interactions between behavioral or psychological factors such as mobility or depression and clinical disorders such as incontinence, heart disease, emphysema or high blood pressure. Others investigate the interactions between behavioral and psychological factors such as work activity or mood and physiological or biochemical responses in normal human subjects.

- Behavioral Physiology Section—
  Bernard T. Engel, Ph.D.

Researchers in this section conduct basic studies in appropriate animal models on the mechanisms mediating the interactions between behavioral factors such as learning or discrimination, and physiological or biochemical factors such as the cardiovascular or pulmonary adjustments to exercise or to cold stress. Others study the influence of aging on the interaction between behavioral and physiological processes.

Laboratory of Personality and Cognition—
Paul T. Costa, Ph.D.

This laboratory emphasizes basic and clinical studies of individual differences in cognitive and personality processes and traits. It also investigates the influence of age on these variables and their reciprocal influence on health, well-being and adaptation. The laboratory employs longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and health-care needs, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

- Cognition Section—
  David L. Arenberg, Ph.D.

Researchers in this section study the psychological mechanisms underlying age-related changes in memory, learning, and reasoning. They seek to determine age-associated changes in verbal learning, memory, problem-solving, information processing, and the relationships between conscious and unconscious information processing. In addition, they analyze the roles of psychological and physiological characteristics in age differences and age changes in cognitive performance.

- Personality, Stress and Coping Section—Paul T. Costa, Ph.D.

This section deals with the dimensions of personality and their influence on processes of adaptation in adult men and women. They determine methods and strategies for coping with the stresses of adult life and evaluate the effects of different coping mechanisms as personality dispositions on such outcomes as subjective well-being, social functioning and physical and psychiatric health. The investigators use epidemiological and longitudinal analyses of personality dimensions to study the interactions of aging with personality and psychological processes.

Laboratory of Cardiovascular Sciences—Edward G. Lakatta, M.D.

Scientists in the laboratory conceptualize and implement original research to describe the influence of age and age-related chronic pathologic conditions on the cardiovascular and myocardial function in man, and in cardiac muscle, myocytes and subcellular organelles in animal models. They also define mechanisms that govern both excitation-coupled functions in nonmuscular tissues and organs. Finally, these scientists determine what factors underlie functional alterations in cardiovascular performance consequent to aging and disease in man and in animal models. Their studies include those on electrophysiological, contractile, biochemical, energetic, pharmacologic, and hormonal determinants of cell function.

- Cardiac Function Sections—
  Edward G. Lakatta, M.D.

This section emphasizes research on cardiac dynamics and cardiac excitation-coupling. Researchers describe the influence of age and age-related chronic pathological conditions in the intact cardiovascular system with special attention to the human myocardium. They normally use noninvasive methodology (e.g., echocardiography, gated blood pool scans, pharmacological probes, and stress) to changes. They also investigate mechanisms that govern excitation and contraction in cardiac tissues and cells and excitation-contraction coupling. Electrophysiological, contractile, biochemical, pharmacologic, and hormonal measurements are used to study aspects of cell functions in isolated cardiac muscle, myocytes, and subcellular organelles and to study the impact of aging and chronic disease states on these mechanisms.

- Energy Metabolism and Bioenergetics Section—Richard G. Hansford, Ph.D.

These investigators study the regulation of substrate oxidation responsible for providing energy in heart muscle and other excitable tissues, as well as the derangement of these central mechanisms which may occur in old age. A special concern is the role of calcium ion as a messenger in this regulation, and the homeostasis of cytoplasmic calcium ion concentration. Isolated cells, nerve terminals, mitochondria, enzymes are the principal objects of these studies.

Laboratory of Molecular Genetics—Edward L. Schneider, M.D.

This laboratory conducts research on the fundamental nature of aging at molecular level. It investigates changes in gene structure and function with aging. Researchers utilize the techniques of molecular genetics to examine age-related alterations in cellular function, and identify, isolate, and characterize genes involved in aging processes and in age--dependent disorders.

Laboratory of Biological Chemistry—Bertram Sacktor, Ph.D.

This laboratory conducts basic research on the molecular basis of life processes. Studies are focused on the

mechanisms of membrane transport, the regulation of these systems by hormones and pharmacological agents, signal-transduction mechanisms, and the changes which occur in aging and in age-associated disorders.

- Regulatory Mechanisms Section—Bertram Sacktor, Ph.D.

This section investigates calcium-phosphate homeostatis, acid-base balance and ion flux in renal, bone, intestinal, and other tissues. Studies related to osteopenia and age concern the factors integrating mineral metabolism and the actions of hormones at the molecular, membrance, and cellular levels. Studies related to the control of intracellular and extracellular environment and metabolism concern the identification, characterization, and regulation of membrane transport systems, largely, but not exclusively in the kidney.

- Membrane Biology Section—Jeffrey Froehlich, M.D.

This section seeks to determine the chemical nature and sequence of intermediate reactions controlling the movement of cations through ionic channels and pumps. The behavior of these systems with respect to energy utilization and energy transduction, ion selectivity, gating mechanisms, and sensitivity to hormones and pharmacological agents is characterized. Studies concern how the affinity, capacity, and selectivity of ion translocation mechanisms are affected by aging.

Laboratory of Cellular and Molecular Biology—
Gunther L. Eichhorn, Ph.D.

This laboratory conducts studies on the biochemistry of aging with studies on the mechanism of fundamental biochemical events that are important in the aging process. Present studies include research into the mechanism of RNA synthesis, age changes in hormonal receptors, age changes in molecular dynamics, and non-invasive magnetic resonance studies of aging in animals and humans.

- Inorganic Biochemistry Section—Gunther L. Eichhorn, Ph.D.

This section is probing the structure of the active site of RNA polymerase in order to understand the mechanism of RNA synthesis. Studies are carried out on the effects of conformational changes in DNA, particularly those induced by metal ions, on genetic information transfer. Effects of metals on aging and Alzheimer's disease are studied. Magnetic resonance is employed for *in vivo* studies of age changes in animals and humans using both spectroscopic and imaging techniques.

- Molecular Physiology and Genetics Section—George S. Roth, Ph.D.

Studies are carried out on the regulation of physiological functions during aging, especially those most critical to life maintenance, as influenced by endocrine, neuro-endocrine, nutritional, environmental, and genetic factors. Particular emphasis is placed on elucidating the molecular and biochemical age changes which occur in the regulatory processes.

- Macromolecular Chemistry Section—Josef Pitha, Ph.D.

Affinity labels for catecholamine receptors are synthesized and evaluated both *in vitro* and *in vivo*. A derivative of the beta-blocker, alprenolol was developed which has the ability to bind irreversibly to beta-adrenoceptors. The compound is used, for example, to compare the rates of synthesis of that receptor in young and old rats. Another emphasis in the section is the design, synthesis, and evaluation of non-toxic solubilizers with the aim of improving oral absorption of hydrophobic hormones and drugs.

- Molecular Dynamics Section—Joseph M. Rifkind, Ph.D.

This section studies the relationship between molecular dynamics and changes in function during aging. Physicochemical methods are used to probe conformational fluctuations of proteins, nucleic acids, membranes, and other cellular components.

Laboratory of Neurosciences—
Stanley I. Rapoport, M.D.

This laboratory investigates the function, structure, physiology, biochemistry, and pharmacology of central and peripheral nervous systems and of muscle, and the changes that take place during

development and aging in animal models and in man.

- Cerebral Physiology and Metabolism Section—Stanley I. Rapoport, M.D.

This section conducts fundamental research on animal models of human aging and disease, as well as collaborative research with the Clinical Section on Brain Aging and Dementia of the laboratory. Areas of concern include neuropharmacology, the blood-brain barrier (ultrastructure, transport, and permeability), peripheral nerve function and morphology, cerebral metabolism, and synaptic transmission. Methods employed in the laboratory include integrative physiological techniques with whole animal preparations, tissue culture and electrophysiology, biochemical and analytical techniques (including HPLC, gas chromatography, mass spectrometry), mathematical modeling in relation to pharmacokinetics, autoradiography of brain structures (with the 2-deoxy-D-glucose technique and techniques to evaluate brain lipid and protein metabolism and blood flow), radiotracer techniques, histology, electromicroscopy, and biophysical approaches to physiology. Broad areas of concern to the neurosciences as they relate to aging and development are addressed.

- Brain Aging and Dementia Section—Robert P. Friedland, M.D.

This section operates a 6-bed Patient Care Unit at the Clinical Center as well as an outpatient Dementia Clinic. Physicians, psychologists, pharmacologists, and physiologists work together in research activities focused primarily on aging of the central nervous system, and on dementia and associated neurological diseases as these relate to the elderly. Aging of men and women, between the ages of 21 and 85, is examined in a longitudinal program with particular emphasis on cognitive function and activity. Patient groups include those with Alzheimer's dementia, multi-infarct dementia, and Down's syndrome, as well as with other relevant central nervous system diseases. Patients are recruited for inpatient protocols via the Dementia Clinic, which also addresses issues of epidemiology and incidence of disease processes. Methods employed include neuropsychometrics, biochemical analyses of neurotransmitters and their metabolites, physiological measurements of activity and neurological competence, and techniques to measure cerebral metabolism and brain structure. Positron emission tomography (PET scanning) is a critical tool of the program, for the examination of cerebral metabolism *in vivo*. The results are correlated with quantitative neuropsychometric evaluation of cognitive and sensorimotor functions.

Particular attention also is paid to the careful clinical evaluation of the noradrenergic and dopaminergic systems through the use of biochemical and pharmacological explorations, in the areas of normal aging, essential hypertension, and related disorders.

The clinical pharmacology of aging is another area of interest for our clinical program and includes the careful evaluation of the pharmacokinetics and pharmacodynamics of various antihypertensive and central nervous system drugs in the elderly.

Research on aging and dementia is frequently conducted in collaboration with other involved clinical and basic groups in other institutes at the NIH on specific areas of common interest. Furthermore, protocols often are designed in collaboration with members of the Basic Section on Cerebral Physiology and Metabolism of the Laboratory of Neurosciences Dementia Clinic, which also addresses issues of epidemiology and incidence of disease processes. Methods employed include neuropsychometrics, biochemical analyses of neurotransmitters and their metabolites, physiological measurements of activity and neurological competence, and techniques to measure cerebral metabolism and brain structure. Positron emission tomography (PET scanning) is a critical tool of the program, for the examination of cerebral metabolism *in vivo*. The results are correlated with quantative neuropsychometric evaluation of cognitive and sensorimotor functions.

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National Institute on Alcohol Abuse and Alcoholism

Alcohol, Drug Abuse, and Mental Health Administration

Robert Niven, M.D.
Director
Laura Rosenthal
Deputy Director of Intramural Research
Markku Linnoila, M.D., Ph.D.
Clinical Director

The National Institute on Alcohol Abuse and Alcoholism conducts an intramural program of basic and applied research on the multiple determinants and processes of alcoholism and other alcohol-derived health problems. The clinical facilities and research laboratories are located at the National Institutes of Health Clinical Center in Bethesda, Maryland. Medical staff fellow appointments are available to conduct clinical and/or basic research investigations. Depending upon the appointment, certain fellows will also have clinical responsibilities.

Appointments in Clinical Research

Medical staff fellowship positions are available in neurology, internal medicine, psychiatry, experimental therapeutics, and developmental neurology. Fellows are appointed for 2 years with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on the NIAAA ward and involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NIAAA research emphases.

Candidates requiring further information about the clinical positions for medical staff fellows should write to Markku Linnoila, M.D., Ph.D., Clinical Director, DICBR, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3B19, National Institutes of Health, Bethesda, Maryland 20892.

Appointments in Laboratory Research

NIAAA medical staff fellow positions are available for laboratory research in the Laboratory of Clinical Studies, Laboratory of Metabolism, and the Laboratory of Preclinical Studies. Appointments are for a 2-year period, with the possibility of extension.

Fellows will engage in research on contemporary biomedical problems. During their tenure, fellows will devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Research experience is gained through the process of personal guidance by senior scientists who are preceptors. Areas of study are developed by each fellow in conjunction with the preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned.

Medical staff fellows have the opportunity to work closely with a diverse group of senior investigators, to participate in courses, conferences and seminars, and to employ advanced research methodologies in the course of their research.

For further information on the NIAAA Medical Staff Fellowship Program, write to the Deputy Director, Intramural Research Program, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3C218, Bethesda, Maryland 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIAAA programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Laboratory of Clinical Studies—
Markku Linnoila, M.D., Ph.D.

The major research interests of the laboratory concern effects of acute and chronic consumption of alcohol in humans. Furthermore, blood relatives of alcoholics at a high risk of developing alcoholism will be compared to age and sex matched subjects without a family history of excessive drinking or alcoholism. The general areas of inquiry are broadly defined by the names of the sections and units in the laboratory: Section of Clinical Science (Peter R. Martin, M.D.); Section of Clinical Brain Research (Michael Eckardt, Ph.D.); Section of Clinical Biochemistry and Pharmacology (Markku Linnoila, M.D., Ph.D.); Section of Analytical Biochemistry (Norman Salem, Ph.D.); Section of Neuroscience (Robert Eskay, Ph.D.); Unit of Genetic Studies (David Goldman, M.D.); and the Unit of Family Studies (Yolande Davenport, M.S.W.). The techniques available include EEG-telemetry, sleep recording, activity and temperature monitoring, evoked responses, brain imaging, neuropsychological testing, advanced computer analyses of blood chemistry profiles, drug concentration measurements with liquid chromatrography, monoamine and neuropeptide analyses with liquid chromatography, membrane lipid analyses with mass fragmentography, receptor studies, and animal behavioral pharmacology. The aims of the program are to test and develop new approaches for the treatment and prevention of alcoholism and its complications as well as to train professionals to work successfully in the field of alcohol research.

Laboratory of Metabolism—
Richard Veech, M.D., D.Sc.

The Laboratory of Metabolism conducts studies in basic biochemistry, clinical metabolic studies on patient samples, genetic studies with fibroblasts, and molecular biology, including studies with recombinant DNA and peptide synthesis. The aim is to provide the most appropriate tehcniques to solve the particular problem at hand.

The basic biomedical studies include the kinetics of alcohol dehydrogenase, PPi-PFK microsomal monooxygenases and the PRPP phosphoribosyl phosphotransferases. Thermodynamic studies are under way covering a number of areas including the purine salvage pathway and the carbonylphosphate synthase reaction. Metabolic studies defining the control points switching amino acids from urea-

genesis to protein synthesis are under way as are studies involving glycogen synthesis, c-AMP and Co effects as well as certain metabolic inhibitors' effects on mitochondrial shuttles. Blood samples from alcoholic patients are examined to determine the nature and source of abnormal metabolites found and the contribution that genetic versus induced enzymatic changes play in inducing these abnormalities. The question is pursued further using cultured fibroblasts from alcoholic and non-alcoholic subjects as well as individuals with a variety of other known genetic diseases.

Finally, peptide fragments and analogues for various pituitary peptides are being synthesized from c-DNA fragments and by solid state peptide synthesizer and are being tested for biological activity.

Laboratory of Preclinical Studies— Forrest F. Weight, M.D.

A broad program of investigation is conducted on physiological, pharmacological, and chemical properties of nervous tissue and the relationship of these properties to the functional activity of the nervous system. Current experimental studies involve two main areas: the physiology and pharmacology of neurons and synapses in the central and peripheral nervous system; and the molecular mechanisms involved in regulating neuronal excitability and membrane permeability in nervous tissue.

Studies on the physiology and pharmacology of neurons and synapses involve primarily electrophysiological techniques such as current-, voltage-, and patch--clamp methods to study the regulation of neuronal excitability and the ionic basis of membrane permeability changes involved in drug and transmitter actions. The general areas studied include: cellular mechanisms regulating membrane excitability; cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin and GABA; membrane mechanisms of neurotransmitter, neurohormone and drug actions; cellular actions of enkephalin, endorphin and other neuropeptides; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbituates, opiates, and other neuroactive substances. Studies are performed primarily on *in vitro* perparations such as CNS slice, sympathetic ganglia, and tissue culture.

Studies of the molecular mechanisms involved in regulating neuronal excitability and membrane permeability employ physical techniques such as fluorescence absorption, polarization and lifetime, and biochemical methods such as gel electrophoresis, column chromatography, ligand binding, and high-voltage electrophoresis to identify, purify, characterize, and study membrane proteins. Studies include investigations on the role of protein phosphorylation, calcium ions, and cyclic nucleotides in the regulation of membrane properties.

National Institute of Allergy and Infectious Diseases

Anthony S. Fauci, M.D.,
Director
John I. Gallin, M.D.,
Director, Intramural Research Program
Michael M. Frank, M.D.,
Clinical Director

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints medical staff fellows for the laboratories described below. Medical staff fellows in the Laboratory of Clinical Investigation and the Laboratory of Immunoregulation begin after at least 1 year of residency training. Fellowship appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation and Laboratory of Immunoregulation carry responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Specific answers to any questions or additional information may be obtained by applicants from the Director, Intramural Research Program, NIAID, National Institutes of Health, Bethesda, MD 20892. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests and information desired.

Clinical Branches

Laboratory of Clinical Investigation—Michael M. Frank, M.D.
Laboratory of Immunoregulation—Anthony S. Fauci, M.D.

The NIAID appoints approximately 9 medical staff fellows. Appointments are made for 3 years and consist of a first year devoted mostly to the care of patients with immunologic, allergic, and infectious diseases and a second and third year devoted primarily to laboratory-based research.

The clinical period is integrated with a program in Clinical Allergy and Immunology that leads to Board eligibility in this sub-specialty. Fellows already certified by the American Board of Internal Medicine may elect to take clinical training in infectious disease that leads to eligibility for the Infectious Disease sub-specialty board of the American Board of Internal Medicine. These programs include exposure to patients with a wide variety of immunologic, allergic, or infectious diseases on the 52-bed NIAID service of the Clinical Center. Clinical experience includes rotations at affiliated hospitals and clinics as well as an extensive formal teaching program involving lecture/seminar series and individual one-on-one teaching. Approximately 7 of the medical staff fellows are appointed to the Laboratory of Clinical Investigation and 2 of the fellows are appointed to the Laboratory of Immunoregulation. The clinical responsibilities are identical for fellows in both laboratories.

The laboratory period consists of a prolonged period of training in one of the research areas currently being pursued in the laboratory. This is under the general preceptorships of the laboratory chief and the senior members of the staff (listed below). Emphasis is placed on the mastery of the knowledge and techniques necessary for a career in basic investigation of diseases

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

Laboratory of Clinical Investigation

- The molecular biology, pathogenesis, and antiviral treatment of human herpes virus infections in man.
- The role of host defense mechanisms in prevention of infections.
- Pathophysiology and treatment of autoimmune hemolytic anemia.
- Pathophysiology and treatment of hereditary angioedema.
  - —The pathophysiology and host defense response to bacteremia.
  - —Host defense mechanisms in systemic mycoses.
- The role of the phagocytic cells in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulation of immune reactivity in normal individuals and in patients with immunologically mediated diseases.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma, allergic diseases such as anaphylaxis, and allergic rhinosinusitis.
- The role of immune complexes in the production of disease.
- Some aspects of immunopathologic mechanisms in parasitic infections.

- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- Laboratory and clinical evaluation of antiviral substances.
- Mechanisms of regulation of mucosal immune responses.
- The pathogenesis of inflammatory bowel diseases.
- The pathogenesis of immunodeficiency diseases.
- The diagnosis and effective management of systemic mastocytosis.

Laboratory of Immunoregulation

- The regulation of human immune responses in normals and in diseases characterized by abnormalities of immune function. Studies include cellular and humoral components, cloning technology, receptor physiology, and molecular biology.
- Study of the immunopathogenic features of immune-mediated diseases and host defense defects.
- Clinical, immunopathogenic, and therapeutic features of the vasculitis syndromes.
- Studies of the clinical manifestations, virology, immunopathogenesis, molecular biology, and therapeutic aspects including immunological reconstitution of the acquired immunodeficiency syndrome (AIDS).
- The molecular biologic approach to gene activation and immunoregulation.
- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.

Further information can be obtained if inquiries with specific questions are addressed to Clinical Director, NIAID.

Research Areas and Senior Staff

Laboratory of Clinical Investigation—
Allergic Diseases—
Michael A. Kaliner, M.D., and
Dean Metcalfe, M.D.
Bacterial Diseases—
John I. Gallin, M.D.
Clinical Immunology—
Michael M. Frank, M.D.,
Eric Brown, M.D.,
Louis Fries, M.D.,
Keith Joiner, M.D., and
Carl Hammer, Ph.D.
Clinical Mycology—
John E. Bennett, M.D.
Kyung J. Kwon-Chung, Ph.D.
Clinical Parasitology—
Franklin A. Neva, M.D.,
Eric A. Ottesen, M.D., and
Theodore Nash, M.D.
Medical Virology—
Stephen Straus, M.D.
Jeffrey Ostrove, Ph.D.
Mucosal Immunity—
Warren Strober, M.D.
Stephen P. James, M.D.
Laboratory of Immunoregulation—
Anthony S. Fauci, M.D.,
H. Clifford Lane, M.D., and
Ulrich K. Siebenlist, Ph.D.

Basic Research Laboratories

Laboratory of Viral Diseases—
Bernard Moss, M.D., Ph.D.

Members of the laboratory conduct basic research on the genetic organization, expression, replication, assembly, and pathogenicity of viruses. In addition, live recombinant viruses are being genetically engineered for use as immunological tools and as vaccines against a variety of infectious agents.

Current research topics include:

- Regulation of gene expression *in vitro* and *in vivo*
- Mechanisms of DNA replication *in vitro* and *in vivo*
- Structure and function of RNA and DNA polymerases
- Genetic engineering of recombinant viruses as live vaccines
- Antiviral agents
- Determinants of virus virulence

- Host resistance genes
- Viral growth factors
- Targets of humoral and cell-mediated immunity

After discussions with members of the laboratory, Medical Staff Fellows choose a research topic and develop experimental protocols. Training in areas of molecular biology, recombinant DNA technology, enzymology, protein chemistry, immunology, tissue culture, and virology is provided during the course of investigations. Progress is monitored informally and by weekly research meetings of the laboratory staff.

Research Areas and Senior Staff
Gene Expression—
Bernard Moss, M.D., Ph.D.
Jerry P. Weir, Ph.D.
DNA Replication—
Mark Challberg, Ph.D.
Frank DeFilippes, Ph.D.
Virus Pathogenesis—
Mark Buller, Ph.D.

Laboratory of Biology of Viruses—
Norman P. Salzman, Ph.D.

The investigations in this laboratory are concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Viral and cellular proteins that regulate transcription and their modes of action are under active investigation. Studies are carried out with both lytic and oncogenic viruses. Fundamental molecular studies are also carried out with uninfected cells.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, and organic chemistry. The program for medical staff fellows is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
Biochemical Virology—
Norman P. Salzman, Ph.D.
Molecular Structure—
James A. Rose, M.D.

Laboratory of Infectious Diseases—
Robert M. Chanock, M.D.

This laboratory's activities are concerned with the basic behavior of viral and mycoplasmal pathogens that play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract, gastrointestinal tract, and hepatic pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as acute gastroenteritis viruses and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological and molecular biological characterization of viruses, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
Epidemiology—
Albert Z. Kapikian, M.D.
Hepatitis Virus—
Robert H. Purcell, M.D.
Molecular Viral Biology—
Ching-Juh Lai, Ph.D.

Respiratory Viruses—
Brian Murphy, Ph.D.

Laboratory of Immunogenetics—
Thomas J. Kindt, Ph.D.

This group is involved in basic research on major gene complexes important in immune function. The approaches used in these studies emphasize structural, serologic, and molecular genetic investigations. The techniques used include quantitative radioimmunoassays, protein structure determinations, recombinant DNA technologies including gene cloning and nucleotide sequencing, assays for DNA regulatory elements, and DNA-mediated gene transfer into mammalian cells; preparation and study of T- and B-cell hybridomas, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on cloning, sequencing, and genetic analyses of genes for rabbit T-cell antigen receptors and MHC products; structural and functional studies on murine H-2 antigens and human HLA antigens; assembly and function of HLA class II antigens and regulation of the class II gene family; regulation of immunoglobulin gene expression during maturation of lymphocytes; and the use of hybridoma antibodies to investigate components of lymphoid cell membranes.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry and molecular biology and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of current concepts concerning the molecular basis of the immune response.

Research Areas and Senior Staff
MHC and TcR Genetics—
T. K. Kindt, Ph.D., and
J. A. Sogn, Ph.D.
Membrane Antigens—
J. E. Coligan, Ph.D.
Molecular Immunogenetics—
E. O. Long, Ph.D.
E. E. Max, M.D., Ph.D.

Laboratory of Immunology—
William E. Paul, M.D.

Scientists in the Laboratory of Immunology are engaged in the study of various aspects of cellular, molecular, and developmental biology of lymphocytes; the regulation of immune responses; immunogenetics; and immunochemistry. Emphasis is placed on developing an understanding of how the various elements of the immune system function normally and of the role of immune mechanisms in the prevention and pathogenesis of diseases.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; molecular genetics, developmental biology, repertoire and specificity of antigen-binding receptors of lymphocytes; and the degree of specialization of individual immunocompetent functional cells. Utilization of many modern techniques in the study of immune responses will be made, including production and use of monoclonal antibodies, cloning and long-term growth of lymphocyte lines; molecular genetic analysis of cells of the immune system; cell biological analysis of lymphocyte activation and differentiation. Medical staff fellows will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
Cellular immunology; cellular and developmental biology of lymphocytes; regulation of the immune response—
Thomas M. Chused, M.D., Ira Green, M.D., William E. Paul, M.D., Ronald H. Schwartz, M.D., Ph.D., Ethan M. Shevach, M.D., and Michail V. Sitkovsky, Ph.D.

Molecular genetics of lymphocytes; immunochemistry—
Ronald N. Germain, M.D., Ph.D.,
John K. Inman, Ph.D.,
Rose G. Mage, Ph.D.,
and David Margulies, M.D., Ph.D.

Laboratory of Microbial Immunity—
Richard Asofsky, M.D.

The laboratory is primarily concerned with the study of basic mechanisms in the responses of lymphocytes to antigens, including microbial antigens.

Several major areas of investigation, each employing a wide variety of immunologic methods, offer the medical staff fellows comprehensive exposure both to the theoretical and technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. Somatic cell hybrids of mouse B lymphocytes, which respond to inducing agents and their unresponsive mutant progeny, are used extensively in this work. The development of T lymphocytes from early precursors to reactive cells is being examined *in vivo* and *in vitro*. Cellular and genetic factors controlling the amplitude and duration of the response to certain bacterial antigens are examined. Methods have been developed for the physical separation of lymphoid cells to obtain functionally purified subpopulations. Finally, factors regulating the development and severity of certain autoimmune diseases, and specific methods of modifying their course are studied in *in vivo* models.

Research Areas and Senior Staff
Experimental Pathology—
Richard Asofsky, M.D.
Microbiology and Immunology—
Phillip J. Baker, Ph.D.

Laboratory of Parasitic Diseases—
Franklin A. Neva, M.D.

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis on those affecting man. A variety of protozoan (malaria, trypanosomes, giardia, leishmania, amebae, and toxoplasma) and helminth (schistosomes, filaria, and strongyloides) parasites are used for experimental work. Current studies include comparative mechanisms of energy transfer, ultrastructure of parasites, and host-parasite interactions *in vitro* and *in vivo*.

Increasing emphasis is being devoted to the immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis, and filiarisis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate, certain problems that can only be investigated in the field are studied in collaboration with institutions overseas. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients are seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, medical staff fellows can select their area of work and a preceptor. In addition, an organized program provides medical staff fellows with an exposure to clinical parasitology.

Research Areas and Senior Staff

Host-Parasite Relations—
A. W. Cheever, M.D.
Cell Biology and Immunology—
F. A. Sher, Ph.D.
Clinical Parasitology—
F. A. Neva, M.D.,
T. E. Nash, M.D., and
E. A. Ottesen, M.D.
Malaria—L. H. Miller, M.D.

Laboratory of Molecular Microbiology—
Malcolm A. Martin, M.D.

This laboratory uses molecular biological techniques to study microorganisms

and their capacity to produce disease in vertebrate hosts. Of prime importance is the biochemical characterization of viral, bacterial, and plasmid genomes and the detailed analysis of DNA segments that regulate the expression of specific gene products.

Programs involving DNA and RNA tumor viruses focus on those portions of the viral genome that encode proteins that initiate and/or maintain the transformed state. The roles of the host cell genetic apparatus and the immunologic system in augmenting the effect(s) of specific viral gene products during oncogenesis are also investigated. Other programs investigate the process of bacterial transformation with special emphasis on the role of plasmids in transferring genetic information from one organism to another.

Biochemical and biophysical techniques, such as molecular cloning, nucleic acid hybridization, and DNA sequencing, are used in combination with procedures such as monoclonal antibody production and immunoprecipitation to answer basic questions involving the structure and function of prokaryotic and eukaryotic genes.

Research Areas and Senior Staff
Biochemical Virology—
Malcolm A. Martin, M.D.
Bacterial Virulence—
Donald LeBlanc, Ph.D.

Rocky Mountain Laboratories—
The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—Bruce W. Chesebro, M.D.

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance, and elimination of persistent viral infections. Particular emphasis is placed on persistent viral infections involving cells of the hemopoietic and lymphoid systems and the central nervous system. The role of persistent infection in the development of autoimmune or immune complex disease is also being studied. Models examined include human AIDS retrovirus, murine, avian and equine retroviruses, rabies virus, Aleutian disease virus of mink, and the scrapie agent.

Research Areas and Senior Staff
Retroviruses—
Bruce Chesebro, M.D., and
John Portis, M.D.
Rabies—
Donald Lodmell, Ph.D.
Aleutian Disease Virus—
Marshall Bloom, M.D.
Scrapie—
Richard Race, D.V.M.
Bruce Chesebro, M.D.
Acute Phase Serum Proteins—
John Coe, M.D.

Laboratory of Microbial Structure and Function—John Swanson, M.D.

Mechanisms of bacterial pathogenicity and virulence are the main foci of study in this laboratory. Bacterial components that mediate interactions with the host are defined and characterized by biochemical and immunochemical techniques; questions relating to expression and regulation of the microorganisms' constituents are approached by molecular cloning, DNA and mRNA sequencing, etc. Protective bacterial immunogens are defined by use of monoclonal antibodies and *E. coli* or salmonellae containing recombinant plasmids, phage, etc., containing the desired bacterial pathogen's genes. Organisms being investigated currently in LMSF include gonococci, chlamydiae, spotted fever rickettsiae, Lyme disease spirochete, and several others. The ability to manipulate intracellular pathogens genetic elements *in vitro* is one long-range goal of LMSF as is identification of potential bacterial vaccines.

Research Areas and Staff—
Chlamydia—Harlan Caldwell, Ph.D.
Gonococci—
John Swanson, M.D.
Rickettsiae—
Robert Anacker, Ph.D.

Laboratory of Pathobiology—
Claude F. Garon, Ph.D.

Members of this laboratory use modern methods of molecular biology in several appropriate model systems to characterize in molecular terms important features of the host-pathogen relation-

ship. The Laboratory of Pathobiology consists of four sections which describe broad areas of interest. The Molecular Pathobiology Section is working on the molecular cloning and expression of genes relevant to the toxic components of *Bordetella pertussis*. The Arthropod-borne Diseases Section concentrates on two tick-borne spirochetes: *Borrelia hermsii*, an agent of relapsing fever, and *Borrelia burgdorferi*, the agent of Lyme disease. The Immunopathology Section is involved in studies on the immunopotentiating actions of crystalline pertussis toxin. The Pathobiology Section is responsible for research utilizing modern methods of transmission and scanning electron microscopy as well as other techniques to define those structural alterations in either tissue or nucleic acids that are related to the pathological condition. An important by-product of these studies is the potential to produce safe and effective vaccines using well defined, pure, perhaps specifically synthesized immunogenic microbial products.

Research Areas and Senior Staff
Nucleic Acid Electron Microscopy—
Claude F. Garon, Ph.D.
Arthropod-borne Diseases—
Alan G. Barbour, M.D.
Molecular Pathobiology—
Jerry M. Keith, Ph.D.
Immunopathology—
John J. Munoz, Ph.D.
Histopathology—
William J. Hadlow, D.V.M.
Medical Entomology—
Willy Burgdorfer, Ph.D.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Pierre F. Renault, M.D.
Acting Director
Jesse Roth, M.D.
Director of Intramural Research
Phillip Gorden, M.D.,
Clinical Director

Appointments in Clinical Research

Each medical staff fellow is assigned to one of the Institute's clinical branches or sections, which he or she carries out both clinical work and laboratory studies. The fellow is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The fellow is encouraged to choose his or her own problem for independent investigation, if facilities, technical advise, and supervision are available. In addition, the fellow provides professional care for research patients admitted to the service of the branch chief and assists in the outpatient department. There is considerable variation among the branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) with respect to the proportion of the fellow's time required for patient care activities.

Medical staff fellows of the Clinical Endocrinology, Diabetes, Metabolic Disease, and Molecular, Cellular, and Nutritional Biology branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIADDK fellows may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new medical staff fellows each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications

and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Phillip Gorden, M.D., Clinical Director, NIADDK, Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20892. Supplementary information sheets on each branch, together with selected bibliographic citations are available on request.

Appointments in Laboratory Research

NIADDK has four positions in laboratory research available each year for medical staff fellows. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research (in some cases, arrangements can be made for an additional year to satisfy specialty board requirements). During their stay here, fellows will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The medical staff fellow, approximately 1 year prior to beginning, will visit NIADDK to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing Jesse Roth, M.D., Director of Intramural Research, NIADDK, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIADDK programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Developing Programs

Programs in clinical and basic research are being developed in NIADDK in the following areas: nephrology, nutrition, and cystic fibrosis. For further information, contact Jesse Roth, M.D., or Phillip Gorden, M.D., Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment for studying the epidemiology of chronic diseases such as diabetes and arthritis among the Pima Indians of Arizona. In addition, clinical research opportunities in the causes, complications, and treatment of diabetes are available at the Phoenix Clinical Research Section in the Phoenix Indian Medical Center. Most candidates complete post-doctoral training before beginning this fellowship. Occasionally, candiates begin the fellowship after completion of an internship. Candidates interested in clinical research are encouraged to write to Clifton Bogardus, M.D., Phoenix Clinical Research Section, 4212 N. 16th Street, Phoenix, Arizona 85016.

Those interested in epidemiology should write Peter H. Bennett, M.D., Epidemiology and Field Studies Branch, NIADDK, 1550 E. Indian School Road, Phoenix, Arizona 85014, for more detailed information.

Clinical Research Branches

Arthritis and Rheumatism Branch—
Henry Metzger, M.D.

- Clinical Coordinator—
  John H. Klippel, M.D.

Branch-wide clinical studies involve patients with lupus erythematosus (especially with nephritis) and with rheumatoid arthritis who are treated with new pharmacologic and apheresis techniques and whose tissues are analyzed to reveal pathogenetic mechanisms.

- Section on Cellular Immunology—
  Alfred D. Steinberg, M.D.

The section conducts studies on the bases for autoimmune diseases in mice and humans with emphasis on systemic lupus erythematosus using classicald genetics, molecular biological and cellular immunological techniques.

- Section on Chemical Immunology—
  Henry Metzger, M.D.

The section conducts fundamental research on the structures and mechanism of action of immunoglobulins and their receptors on cells, using protein immuno- and membrane-chemistry, and cell biological techniques.

- Section on Connective Tissue Disease—
  Paul H. Plotz, M.D.,
  James Balow, M.D., and
  Ronald L. Wilder, M.D., Ph.D.

This section studies the etiologic and pathogenetic basis of autoimmunity (lupus, psoriatic arthritis, rheumatoid arthritis, polymyositis) by investigations of patients and animals. The role of viruses and bacteria in these illnesses is studied, using cellular, molecular biological, immunological, and pharmacological techniques.

Clinical Endocrinology Branch—
Jacob Robbins, M.D., Jan Wolff, M.D., Ph.D., and Harold Edelhoch, Ph.D.

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid hormones. Laboratory research encompasses fundamental and applied protein chemistry, including studies on hormone transport proteins, hormone metabolism, the mechanism of hormone actions, control mechanisms in secretory cells, adenylate cyclase-receptor interactions and membrane biochemistry.

Molecular, Cellular and Nutritional Endocrinology Branch
Molecular Regulation and Neuroendocrinology Section—
Bruce D. Weintraub, M.D., and
Irwin M. Chaiken, Ph.D.

This section conducts basic and clinical investigations on the regulation of hypothalamic, pituitary, and placental polypeptide hormones. Current studies focus on the regulation of transcription, glycosylation, secretion and action of thyrotropin, gonadotropins, and vasopressin in various cell lines, animal models, and patients. A number of *in vivo* techniques are employed in both animals and patients, and a wide variety of *in vitro* techniques are applied from the areas of molecular and cell biology, neuroendocrinology, biochemistry, and hormone action. Clinical investigations are related to disorders of the hypothalamus, pituitary and thyroid, particularly involving thyrotropin-releasing hormone, thyrotropin, and thyroid hormone action.

Experimental Diabetes, Metabolism and Nutrition Section—
Samuel W. Cushman, Ph.D., and
Ian A. Simpson, Ph.D.

This section (1) investigates the structure, fuction and biosynthesis of integral membrane proteins involved in the hormonal regulation of carbohydrate and lipid metabolism, especially the receptors for insulin and insulin-like growth factor II, and the glucose transporter; (2) studies the molecular and cellular basis of hormone action, especially relating to the mechanism of insulin action and its counterregulation by catecholamines,

other peptide hormones, and the glucocorticoids; and (3) examines the influence of altered metabolic and nutritional states on cellular function and its regulation by hormones, especially those states associated with perturbed insulin action such as diabetes, obesity, and altered dietary carbohydrate and fat intake.

Growth and Development Section—
Matthew M. Rechler, M.D.

The mission of this section is to understand the mechanisms by which hormonal, nutritional, and cellular factors interact to regulate cell growth in different physiological states (i.e., fetal/embryonic development, post-natal growth, wound repair, neural cell growth and maintenance), and how these controlled processes become deranged in pathological states involving excessive or inadequate cell growth (e.g., intrauterine growth retardation, dwarfism, neoplasia, atherosclerosis, diabetic retinopathy). The biosynthesis and action of polypeptide hormones/growth factors and their regulation will be studied in appropriate model systems (e.g., cell cultures established from human subjects and animals), using state-of-the-art techniques of molecular and cell biology. Special emphasis will be given to interactions between different cell types and their products, to regulation of tissue responsiveness to growth factors, and to alternative expression of growth factor genes resulting in novel peptides with biological functions not directly related to cell growth.

Clinical Hematology Branch—
N. Raphael Shulman, M.D.

Laboratory work concerns problems in the fields of immunohematology, platelet physiology and metabolism, and blood coagulation. Current interests include mechanisms of immune cellular injury involving drug-, allo-, and auto-antibodies, correlation of platelet metabolism and membrane reactions with function, and interrelationships between cellular and humoral factors in hemostasis. Clinical work involves patients with immunologic and hemorrhagic disorders relevant to laboratory studies.

Diabetes Branch—
Phillip Gorden, M.D., Jesse Roth, M.D., Simeon Taylor, M.D., Ph.D., and Derek LeRoith, M.D., Ph.D.

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors in disease states, receptor antibodies, and genetic disorders of glucose metabolism, isolation and characterization of receptor components, the role of receptors in hormone and drug action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects include insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, somatostatin, an other peptide messenger molecules; and their role in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

Digestive Diseases Branch—

- Section on Gastroenterology—
  Jerry D. Gardner, M.D., and
  Robert T. Jensen, M.D.

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunologic processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Liver Diseases Section—
  E. Anthony Jones, M.D., and
  Jay H. Hoofnagle, M.D.

Programs are concerned with research into hepatic physiology, immunology, and disease. Laboratory research projects include studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and other chronic liver diseases; investigations of the significance of various viral antigens and antibodies in chronic type B hepatitis, characterization of cell-surface

receptors on isolated hepatocytes, Kupffer cells, and hepatic endothelial cells; and the evaluation of the pathogenetic mechanisms that mediate the encephalopathy in an animal model of fulminant hepatic failure. Clinical investigations include trials of interferon and other antiviral agents in the treatment of chronic type B hepatitis, chronic delta hepatitus and chronic non-A, non-B hepatitis, and a controlled trial of immunosuppressive therapy in primary biliary cirrhosis.

Genetics and Biochemistry Branch—
R. Daniel Camerini-Otero, M.D., Ph.D.,
April Robbins, Ph.D., Richard Proia, Ph.D.,
and Eric Ackerman, Ph.D.

The branch conducts studies in clinical, biochemical, developmental and molecular genetics. The range of current projects covers a wide field from the very basic (*e.g.,* mechanisms of genetic recombination and gene conversion in mammalian cells, DNA-mediated gene transfer, the regulation of gene expression, the molecular biology of early development in *Xenopus laevis,* biosynthesis and transport of lysosomal proteins, the molecular mechanisms of endocytosis and the biochemical and molecular bases of human genetic disorders) to the more applied (development of new diagnostic tests and carrier detection for a number of human genetic diseases and the development of new techniques for gene purification and transfer).

Medical staff fellows seeking training in medical genetics may apply to this branch and participate in the NIH Interinstitute Medical Genetics Program (see page 6). The program fulfills all the requirements of the American Board of Medical Genetics and completion of a genetics fellowship in this program leads to board eligibility in this subspecialty. Candidates must have training in a medical specialty such as internal medicine or pediatrics.

Laboratory of Chemical Biology—
Alan N. Schechter, M.D.

The clinical focus of this section is on the pathophysiology of the hemoglobinopathies and other red cell diseases. Basic studies are concentrated on using NMR, cell separation and molecular genetic techniques to examine molecular interactions and metabolic processes in normal and abnormal erythrocytes and human erythroid cells. Several clinical protocols are designed to develop non-invasive methods, including laser-Doppler velocimetry, NMR and other imaging modalities, to assess the severity of sickle cell anemia and to follow the results of therapy. The section participates in the NIH Interinstitute Clinical Genetics Program. (For non-clinical studies see Basic Research Laboratory listing.)

Metabolic Diseases Branch—
Gerald D. Aurbach, M.D.,
Stephen J. Marx, M.D., and
Allen M. Spiegel, M.D.

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone, and calcitonin. A family of guanine nucleotide binding proteins, including those associated with adenylate cyclase, transducin (a retinal photo-receptor protein), and the products of the RAS oncogenes are being studied with immunochemical and molecular biologic techniques.

The clinical program involves studies of patients with disorders of mineral metabolism. These include patients with hereditary resistance to parathyroid hormone or to calciferols. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is used for *in vitro* studies on control of hormone secretion.

Phoenix Clinical Research Section—
Clifton Bogardus, M.D.,
Barbara V. Howard, Ph.D.,
and Peter H. Bennett, M.B.

This section is currently involved in studies of diseases particularly prevalent among southwestern American Indians. One of the major areas under investigation is diabetes mellitus in the Pima

Indian population. This group has the world's highest reported prevalence of type II (noninsulin dependent) diabetes. The geographical proximity of this unique population to the Phoenix area provides an excellent opportunity for insight into the causes and complications of type II diabetes. A problem closely related to the diabetes in this group is that of obesity. These areas are under intensive scientific investigation in both the 24-bed clinical research unit and the basic science research laboratory which are co-located within the Indian Health Service Referral Hospital, Phoenix, Arizona.

Clinical studies currently in progress include whole-body insulin resistance, nutrition-induced alterations in metabolism, lipid and lipoprotein metabolism, and dietary and exercise therapy in the treatment of diabetic patients. The laboratory research is centered around insulin-mediated glucose metabolism in adipocytes from diabetic and nondiabetic donors, fat cell metabolism, as well as a variety of studies supporting the clinical investigations.

Close collaboration with the Epidemiology and Field Studies Section allows investigation into the prevalence of not only diabetes and obesity, but also cardiovascular disease, gallbladder disease, lipid and lipoprotein abnormalities, and rheumatoid arthritis in the Pima Indians.

Southwestern Field Studies Section
William C. Knowler, M.D.,
David J. Pettitt, M.D., and
Peter H. Bennett, M.B.

This section, located in Phoenix, Arizona, conducts research in the etiology of diabetes and its associated risk factors, genetic determinants, vascular complications, and natural history in the 20-year longitudinal study among the Pima Indians of Arizona. Staff fellows participate in data collection and monitoring, and in analysis and publication of results from this study. They may also engage in activities relating to the design, monitoring or analysis of clinical trials in the field of diabetes and its complications. The section has additional activities in the epidemiology of arthritis, and renal, metabolic and digestive diseases, such as gallbladder disease. Staff of the section may also collaborate with the Phoenix Clinical Research Section, NIADDK, on in-patient metabolic studies related to diabetes, obesity, and lipoprotein metabolism.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—
Herbert Tabor, M.D.,
Simon Black, Ph.D.,
Anthony Furano, M.D.,
Victor Ginsburg, Ph.D.,
Leonard D. Kohn, M.D.,
Nancy Nossal, Ph.D., and
Reed B. Wickner, M.D.

The work of this laboratory includes a large variety of biochemical, genetic, and molecular biological investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, and yeast and *Escherichia coli* genetics. Studies are also carried out on developmental biology and genomic structure and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these members to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance.

A third section is concerned with the biology and immunology of the complex carbohydrates of animal cell surfaces.

A fourth section is studying the genetic control of replication of a double-stranded RNA virus of yeast and other

problems in the genetics of simple eukaryotes.

Laboratory of Biochemistry and Metabolism—
G. Gilbert Ashwell, M.D.,
William B. Jakoby, Ph.D.,
Leonard D. Kohn, M.D., and
Yale J. Topper, Ph.D.

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes an examination of the hormone-dependent differentiation and development of mammary gland tissue in normal and hypophysectomized rats; a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; studies on the mechanism of receptor-mediated endocytosis and glycoprotein-membrane sorting in eukaryotes; using biochemical methods as well as those of somatic cell mutation; study of the cluster of enzymatic activities classified as enzymes of detoxification that function in the conjugation of foreign compounds in mammals; and a study of structure and function of cell membranes and their interaction with hormones, toxins and neurotransmitters, both normally and in autoimmune thyroid disease. In addition to the above general areas, specific projects of individual investigators include a study of the enzymes involved in carbohydrate metabolism, biochemical abnormalities in human cystinosis, DNA interactions with proteins as analyzed by the methods of genetic engineering, and thermodynamic and kinetic studies on enzymatic and protein-folding mechanisms.

Laboratory of Bioorganic Chemistry—
John W. Daly, Ph.D.,
Donald M. Jerina, Ph.D., and
Phil Skolnick, Ph.D.

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of action or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathologic function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, central stimulants, depressants, tranquilizers, anxiolytics, and other therapeutic agents, toxins, carcinogens, and mutagens.

Laboratory of Chemical Biology—
Alan N. Schechter, M.D.,
Hiroshi Taniuchi, M.D., Ph.D., and
Adrian Parsegian, Ph.D.

Research in this laboratory is focused on the control of gene expression, on the folding of proteins, and on the forces stabilizing macromolecules. Dr. Schechter and his group are studying the control of hemoglobin synthesis, using molecular genetic techniques in cultured human erythroid cells. The work includes studies of the *cis* and *trans*-acting factors that affect transcription and translation. In addition, biophysical methods, especially NMR spectroscopy, are being used to study molecular interactions inside erythrocytes, including the polymerization of sickle hemoglobin. Dr. Taniuchi and his colleagues are studying the folding and dynamics of proteins, using cytochrome *c* as a model, with a variety of chemical and physical techniques, including peptide synthesis and NMR. Dr. Parsegian and his group are studying the molecular forces that stabilize protein assemblies, nucleic acids and membrane pores.

Laboratory of Chemical Physics—
Edwin D. Becker, Ph.D., Elliot Charney, Ph.D., William A. Eaton, M.D., Ph.D., William A. Hagins, M.D., Ph.D., and Ira W. Levin, Ph.D.

Research in this laboratory is characterized by the application of modern physical techniques to the study of a wide range of biological problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S, study of the association of mononucleotides and of the conformational behavior of polynucleotides, investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes, analysis of excited electronic states of small molecules in the vapor phase and in molecular beams, development of methods for asymmetric synthesis, study of the structural characteristics of model membrane systems, the structure and dynamic behavior of nucleic acids and nucleoproteins, and the dynamics of ligand binding and structural changes in hemoglobin. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism, ultraviolet and visible microspectrophotometry, and time-resolved absorption spectroscopy with nanosecond lasers.

Laboratory of Chemistry—
Bernhard Witkop, Ph.D., Sc.D., Louis A. Cohen, Ph.D., Arnold Brossi, Ph.D., Cornelius P. J. Glaudemans, Ph.D., and David F. Johnson, Ph.D.

In the oldest laboratory of the Institute (founded June 20, 1905), chemistry is represented in its broadest context in five independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, steroid hormones, immunochemistry, novel toxins, metabolism, antiviral agents, interferon, and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder cancer, effects of novel colchicine derivatives on microtubules, affinity labeling of glucocorticoid receptors, separation of addictive from analgesic properties in new synthetic morphine substitutes, characterization of sodium channels in electrogenic membranes by a frog toxin, the acetylcholine receptor, development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes, hypoxic cell sensitizers, cytotoxic agents selective for cancer cells, the interaction between antigens and monoclonal antibodies, recombinant hybrid immunoglobulins and the detailed structure of fungal antigens, and chemistry and biochemistry of interferon induction and interferon-related enzymes.

Laboratory of Cell Biology and Genetics—
Harvey B. Pollard, M.D., Ph.D., Eduardo Rojas, Ph.D., Illoni Atwater, Ph.D., Barrie J. Carter, Ph.D., Loretta Leive, Ph.D., Ned Feder, M.D., and Joe-Hin Tjio, Ph.D.

The laboratory carries out basic studies and collaborative clinical studies relating to mechanisms regulating secretion of hormones and transmitters from endocrine nerve and endothelial cells. Other work includes analysis of endocytosis and phagocytosis by macrophages and macrophage cell lines, structure of nerve and other cell types by both light and electronmicroscopy, immunology and cytogenetics of autoimmunity, and of the molecular biology of viral genomes.

Laboratory of Molecular Biology—
Martin Gellert, Ph.D., Jun-ichi Tomizawa, Ph.D., Gary Felsenfeld, Ph.D., David R. Davies, Ph.D., Robert Martin, Ph.D., H. Todd Miles, Ph.D., and Terrell Hill, Ph.D.

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters), and studies of the mechanism of hemoglobin S gelation, the phenomenon that causes sickling of red blood cells in sickle cell anemia. Other investigations are concerned with the structure

and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Cellular and Developmental Biology—
Robert T. Simpson, M.D., Ph.D., Martin Rodbell, Ph.D., Bernard T. Kaufman, Ph.D., and Robert O. Scow, M.D.

This laboratory consists of four sections devoted to various biochemical and physiological investigations. The Section on Endocrinology investigates hormonal regulation of enzymes involved in chylomicron uptake and metabolism in adipose and mammary tissues, the influence of hormones on cellular development and metabolism, and the disposition of fat and metabolites in the cell as viewed from ultrastructural studies. The Section on Nutritional Biochemistry investigates the structural and functional aspects of dihydrofolic reductase and other enzymes involved in folic acid metabolism and the intermediary metabolism of lipids, carbohydrates, and amino acids in the small intestine. The Section on Membrane Regulation studies the mechanism of action of hormones on adenylate cyclase and other membrane regulatory processes. The Section on Developmental Biochemistry investigates the structure and function of chromatin and the regulation of gene function during development.

Laboratory of Physical Biology—
R. J. Podolsky, Ph.D., and J. Buck, Ph.D.

This laboratory carries out a broad range of studies. The mechanism of muscle contraction is studied in intact cells and in simplified preparations, using time-resolved X-ray diffraction in conjunction with mechanochemical techniques. Activation of muscle cells is examined by measuring calcium movement between the myofilaments and the sarcoplasmic reticulum in skinned muscle fibers. Lipid dispersions in water are investigated as models of the structure and physical states of lipids in cell membranes. The actions of ionizing radiation on macromolecules are used to determine the *in vivo* size of the functional units for different biological activities (hormone receptors, enzyme complexes, and regulatory units). Electron microscopy is carried out with a wide variety of preparations, and digital image processing techniques are used to enhance resolution. Other subjects under investigation are enzyme organization in unicellular organisms, metamorphosis in insects, human red cell sickling, and biological rhythms and entrainment.

Mathematical Research Branch—
John Rinzel, Ph.D.

The branch conducts research on the mathematical and theoretical aspects of biological problems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level, electrotonus in neuronal dendritic systems, excitability and auto-rhythmicity in neuroelectric signaling, bifurcation, and stability studies of nerve conduction and diffusion-reaction systems, nonlinear chemical/biochemical oscillations, analysis of nucleic and amino acid sequences, and mathematical modeling of renal functions.

National Institute of Child Health and Human Development

Duane Alexander, M.D.,
Director
Arthur S. Levine, M.D.,
Scientific Director, (Director, Intramural Research)
D. Lynn Loriaux, M.D., Ph.D.,
Clinical Director

The Intramural Research Program is broadly concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. In addition to four major clinical research and training programs in the areas of genetics and endocrinology, a diversity of developmental models are under study in twelve fundamental research laboratories, drawing upon observations in bacteria, *Drosophila,* yeasts, viruses, molluscs, frogs, rodents, and subhuman primates. Disciplines employed in these studies include biochemistry, virology, molecular biology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics, mathematical and theoretical biology, reproductive physiology and developmental psychology.

Each medical staff fellow will devote time mainly to research in the laboratory under the supervision of a senior preceptor. Each is expected to engage in appropriate course work in the basic and/or medical sciences as well as tutorial seminars, and to take an active part in the journal club, lecture series, and other laboratory exercises.

All appointments as medical staff fellows are for a minimum of 2 years with a third optional year. Most fellows elect to remain for 3 full years and are offered this opportunity. For a limited number of highly qualified fellows, additional years of training are possible.

The Intramural Research Program's twelve branches and laboratories are each under the direction of a branch or laboratory chief. Medical staff fellow positions are usually available in all of these areas. The fellows have an exceptional opportunity to become independent scientists in a field of their interest, and to prepare themselves for a career in academic medicine and research.

Prospective applicants wishing further information should write to Arthur S. Levine, M.D., Scientific Director, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892. In writing, please be specific as to your interests and the information you require.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research.

Medical staff fellows will be responsible, under the guidance of senior investigators on the NICHD staff, for the primary medical care of research patients during the first year of their service. During this time, they will serve in the medical services that are associated with the clinically oriented branches of the Institute and assist in the work of the service with inpatient care, consultation and in the outpatient department. The clinical period offers exposure to rich case material and to highly sophisticated approaches to clinical investigation.

The fellow devotes the subsequent time to laboratory research under direction of a senior preceptor in any one of the twelve Institute laboratories. The choice of laboratory is made during the fellow's first 6 months at NIH. No clinical responsibilities are required during

the second or additional years for fellows who have chosen nonclinical laboratories.

The NICHD selects nine medical staff fellows each year who participate in one of the four approved clinical subspecialty training programs sponsored by this Institute: adult endocrinology, pediatric endocrinology, gynecologic endocrinology, and medical genetics.

Fellows in adult endocrinology apply to the Developmental Endocrinology Branch and participate in the NIH Joint (inter-institute) Endocrinology Fellowship Program which leads to board certification by the American Board of Internal Medicine in the subspecialty of endocrinology and metabolism (see page 5). Applicants must be board eligible in the specialty of internal medicine prior to the initiation of the fellowship. The first year of the fellowship is primarily clinical. Further years are devoted to a research project which may be carried out in any of the twelve branches or laboratories of the NICHD.

Applicants for the pediatric endocrinology fellowship also apply to the Developmental Endocrinology Branch and must have completed PL-3 level training prior to the initiation of the fellowship. The first year is primarily clinical, with pediatric patient care responsibilities in the three endocrinology units associated with the NIH Joint Endocrinology Fellowship Program. The further years are spent in any one of the branches or laboratories of NICHD. This fellowship may lead to approval by the American Board of Pediatrics for board certification in the subspecialty of pediatric endocrinology.

Applicants for the gynecologic endocrinology fellowship apply to the Office of the Scientific Director and must have completed an accredited residency in obstetrics and gynecology prior to the first fellowship year. The fellowship is a cooperative program utilizing the combined clinical facilities of the NIH, the National Naval Medical Center, and the Walter Reed Army Medical Center. The first year is entirely clinical, 6 months being spent on the combined endocrine services of the NIH, and 6 months in the infertility clinics of the two Service hospitals. The following years of the fellowship are spent in a research program that may be undertaken in any of the branches or laboratories of the NICHD. This program is recognized by the American Board of Obstetrics and Gynecology and leads to certification in the subspecialty of gynecologic endocrinology.

Fellows in medical genetics apply to the Human Genetics Branch and participate in the NIH Interinstitute Medical Genetics program (see page 6). The program fulfills all of the requirements proposed by the American Board of Medical Genetics and leads to board certification in this subspecialty. Candidates may be pediatricians or internists, and occasionally represent other medical specialties such as neurology and obstetrics. As with the other NICHD clinical specialty programs, the first year of the fellowship is primarily clinical, with patient care responsibilities on the research wards, in the NIH, Johns Hopkins, and Children's Hospital Genetics Clinics and in the NIH-supervised Prenatal Diagnosis Clinic at George Washington University Hospital. The further years are spent in a research program in any NICHD laboratory or branch of the fellow's choice.

Applications for all four of these programs are considered 1 or 2 years in advance of the proposed starting date. Application forms may be obtained from the NIH Medical Staff Fellowship Office, Building 10, Room 2N226, National Institutes of Health, Bethesda, Maryland 20892.

Appointments in Laboratory Research

A limited number of appointments are available which are designed to give highly qualified physicians an opportunity to do basic research in any area of the Institute under the direct supervision of a senior preceptor. Usually physicians enter the appointment after completing

internship and at least 1 year of residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises. Fellows with this appointment work exclusively with the branch or laboratory in which they are accepted, and make this choice at the time of initial application.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate School of the Foundation for Advanced Education in the Sciences, Inc. Medical staff fellows are expected to take advantage of this academic work. (See page 143).

Medical Staff Fellows in Pharmacology (PRAT)

Several of the NICHD laboratories and branches participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program see page 88.

Clinical Research Branches

Developmental Endocrinology Branch—D. Lynn Loriaux, M.D., Ph.D.

The endocrine concomitants of normal and abnormal human growth, development, and differentiation are examined in this branch. Specific areas of study include the mechanisms underlying the initiation of puberty; the regulatory physiology and biochemistry of the glycoprotein hormones; the roles of sex steroid hormones, growth hormones, and other growth factors in bone growth; and the physiology and biochemistry of the action of hypothalamic releasing hormones. Clinical research on male and female reproductive disorders is also a major interest of this branch.

- Section on Steroid Hormones—D. Lynn Loriaux, M.D., Ph.D.

The mechanism of action of the steroid hormones is under investigation, including studies of the clinical disorders of masculinization, feminization, and glucocorticoid deficiency or excess. In this regard, patients with polycystic ovarian disease, gynecomastia, polyendocrine deficiency, and Cushing's syndrome play an important role in the clinical research program of the branch. Two syndromes of resistance to steroid hormone action, testicular feminization and cortisol resistance, are under intensive study as well.

- Section on Developmental Endocrinology—Gordon B. Cutler, M.D.

This section studies the pathophysiology of the syndromes of precocious and delayed puberty and the treatment of these disorders, including the use of LHRH agonist analogues. The section also examines the role of sex steroid hormones in long bone growth, and is exploring the treatment of disorders of stature with agents such as sex steroids, growth hormone, and hypothalamic releasing hormones.

- Section on Medical Endocrinology—Bruce C. Nisula, M.D.

The glycoprotein hormones, TSH, LH, FSH, and hCG, are the subjects of both clinical and basic research studies, and understanding the physiology of regulation of TSH, LH, and FSH secretion by the pituitary is a major goal. The development of new diagnostic procedures involving the glycoprotein hormones and evaluation of their clinical applications is emphasized. Clinical disorders of thyroid function and conditions characterized by abnormal glycoprotein hormone secretion are being studied to

elucidate the role of molecular heterogeneity in these situations. The regulation of thyroid function through the TSH receptor-adenylate cyclase system is of particular interest.

- Section on Reproductive Endocrinology—
  Richard J. Sherins, M.D.

Human reproduction is the major area of interest in this section. The hormonal control of gonadal development and the basic physiology of gametogenesis are investigated. Clinical investigations on the full range of male and female gonadal disorders, and especially infertility, are aimed at understanding pathogenetic mechanisms and developing new therapeutic modalities.

Human Genetics Branch—
Michael A. Zasloff, M.D., Ph.D.

The Human Genetics Branch's interests range from studies on the etiology, diagnosis, and treatment of genetic and developmental disorders of young people to very basic studies on eukaryotic gene expression utilizing recombinant DNA methodology. There is a broad attempt to apply "genetic engineering" together with tissue transplantation techniques to therapeutic strategies. The intent of the Branch's clinical fellowship program is to provide wide exposure to the field of human genetics, including clinical care, clinical research, and basic studies. Current research projects concern genetic disorders of lipid and carbohydrate metabolism, the mucopolysaccharidoses, heritable disorders of bone and connective tissue, lysosomal storage diseases (e.g., cystinosis), temperature-sensitive models of cellular differentiation, the genetics of alcohol-related syndromes, and the structure and function of human tRNA genes.

- Section on Cellular Differentiation—
  Janice Chou, Ph.D.

This section conducts research on the mechanisms of gene function and regulation during mammalian cell differentiation. Major emphasis is on the investigation of biochemical and molecular changes associated with normal and abnormal differentiation processes. Techniques utilized include tissue and organ culture, and recombinant DNA methodology.

- Section on Developmental Genetics—
  Anil Mukherjee, M.D., Ph.D.

This section emphasizes biochemical, cellular, and immunological studies on early mammalian development. Special emphasis is given to the study of a progesterone dependent, immunosuppressive protein, uteroglobin. Additionally, basic and clinical investigations are being conducted to understand the etiology of fetal alcohol syndrome. Techniques utilized include tissue culture, radioreceptor assays, electrofocusing, and various methods of protein purification and characterization.

- Section on Disorders of Carbohydrate Metabolism—
  James B. Sidbury, M.D.

This section focuses on the natural history, diagnosis, treatment and pathophysiology of genetic disorders of carbohydrate metabolism, with a special emphasis on the Prader-Willi Syndrome, galactosemia, and the glycogen storage disorders.

- Section on Biochemical Genetics—
  William Gahl, M.D., Ph.D., Acting

A combination of clinical and laboratory-based research is used to identify the biochemical etiology of genetic diseases such as cystinosis, gluthathione defects, the mucopolysaccharidoses, and rare disorders of bone and connective tissue such as osteogenesis imperfecta and fibrodysplasia ossificans progressiva. Both biochemical and molecular biological techniques are employed. Emphasis is also placed on the development of new methods of prenatal diagnosis, the detection of heterozygotes, and treatment.

- Section on Molecular Biology—
  Michael A. Zasloff, M.D., Ph.D.

This section studies basic mechanisms of eukaryotic gene expression as a means of understanding disease processes. Current studies include genomic organization and expression of human tRNA genes, the mechanism of nuclear RNA transport and RNA processing. Techniques utilized include recombinant DNA methodology, amphibian oocyte injection, and DNA transfer into somatic cells.

Laboratory of Comparative Ethology—
Stephen J. Suomi, Ph.D.

Research in this laboratory is focused on the development of behavior in humans, primates, and other animal models. The interactions of genetic and environmental factors are explored, using a comparative mammalian approach, so as to determine the origins and evolution of various behavioral phenotypes. Experimental results in animals are correlated with the results of longitudinal studies in human infants and families. At the same time, hypotheses concerning behavior in the animal models are correlated with results obtained by physiological and molecular neuroscience techniques.

- Section on Comparative Behavioral Genetics—
  Stephen J. Suomi, Ph.D.

  This section studies genetic and environmental interactions through comparative ontogenic study of rhesus monkeys and other animals (living under semi-natural conditions). The neuroanatomical, electrophysiological, and biochemical concomitants of various behavioral phenotypes are determined, and these phenotypes are tracked developmentally from birth through senescence. Monkeys bred to yield specific behaviors under stress (*e.g.*, "laid back" or "uptight") are used extensively in these longitudinal investigations.

- Section on Brain, Behavior and Communication—
  David Symmes, Ph.D.

  The focus of interest is on vocal communication, learning, and play among subhuman primates, and the relationship of these behaviors to those of humans. Study of monkeys living in social structures and within naturalistic habitats is an important aspect of research on vocal communication. The section also utilizes neurophysiological and neuropharmacological techniques to study coding of natural sounds in the CNS, and to elucidate the mechanisms of vocal production.

- Section on Child and Family Research—
  Frank A. Pedersen, Ph.D.

  This section investigates early influences on the development of human behavior and personality. These studies are undertaken within the context of family and cultural structures. Factors in the home that influence cognitive and motivational development are being explored, such as the events surrounding childbirth, the infant's separation experiences, and maternal employment. All of these studies are longitudinal in design.

Basic Research Laboratories

Office of the Scientific Director—

- Section on Growth Factors—
  Gordon Guroff, Ph.D.

  This section studies the biochemical and physiological actions of nerve growth factor, a peptide required for the development of the sympathetic and sensory nervous systems. Reagents include the PC12 cell, a clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. Phosphorylative events and changes in gene transcription which may underlie differentiation are being studied to define the exact molecular mechanism by which such peptide factors act.

- Section on Viruses and Cellular Biology—
  Arthur S. Levine, M.D.

  DNA viruses which influence differentiation are used to probe the developmental program of macromolecules (*e.g.*, *onc* gene products) that regulate changes in the phenotypes of normal and transformed animal cells. The DNA viruses are also utilized as models in studies on mammalian mutagenesis and DNA repair/replication. The techniques of virology, tissue culture, somatic cell hybridization, molecular biology, and immunology are employed.

Laboratory of Developmental Neurobiology—
Phillip G. Nelson, M.D., Ph.D.

The neurobiologic mechanisms relevant to development of the nervous system are investigated with emphasis on studies at the cellular membrane and molecular levels. The basis for short- and long-term interaction between nerve cells

is studied electrophysiologically and biochemically. Combined molecular and morphological methods are used in the analysis of experiential modifications of brain function and gene expression.

- Section on Neurobiology—
  Phillip G. Nelson, M.D., Ph.D.

Tissue-cultured neural and muscle tissue are studied, using intra-cellular electrophysiologic techniques and correlative light and electron microscopic morphologic methods. Neuropharmacological studies of pre- and post-synaptic receptors involve voltage-clamp and patch-electrode techniques. Studies of cholinergic function and neurodifferentiation employ molecular genetic, biochemical, and monoclonal antibody methods. Long-term interactions between nerve and muscle, and the influence of electrical activity on neural development, are of particular interest. Molecular biologic techniques are being used to study gene expression during nervous system development.

- Section on Neuroendocrinology—
  David C. Klein, Ph.D.

Investigations focus on the molecular mechanisms through which neurotransmitters regulate gene expression. Cultured pinealocytes are the primary experimental model. Current areas of study include the adrenergic control of pineal cyclic AMP and cyclic GMP, and the role of membrane protein phosphorylation in transsynaptic signal transduction. Recombinant DNA techniques are being used to study the regulation of enzymes involved in the conversion of tryptophan to melatonin.

Laboratory of Neurochemistry and Neuroimmunology—
Harold Gainer, Ph.D.

This laboratory utilizes the tools of molecular biology and immunology in a cell biological context to study the biosynthesis, packaging, transport, and secretion of biologically active neural peptides and proteins. Various model neuronal systems in organisms ranging from molluscs (squid) to vertebrates (e.g., frog, chick, and rat) are used to examine the development and function of defined neural pathways *in vivo*. Organotypic cultures of these systems are also studied. Techniques which are used include peptide chemistry, monoclonal antibodies and immunochemistry, light and electron microscopy, immunohistochemistry and cytochemistry, subcellular fractionation, and tissue culture.

- Section on Functional Neurochemistry—
  Harold Gainer, Ph.D.

This section focuses on the development and functional organization of peptidergic neurons in the hypothalamus. This includes consideration of the extracellular mechanisms involved in the regulation of specific peptide biosynthesis, as well as secretory vesicle interactions with calcium-binding and cytoskeletal proteins during secretion and neurite outgrowth. Characterizations of specific proteins within these neurons by correlative ultrastructural and immunochemical techniques are made, and the functional roles of these proteins are investigated in both developing and mature neurons.

- Section on Cellular Neurobiology—
  Y. Peng Loh, Ph.D.

This section investigates the regulation and mechanism of biosynthesis of neuropeptides, at the transcriptional, translational and post-translational levels, in correlation with different physiological and developmental states in the animal model. The primary focus is on the ACTH/endorphin/**a**-MSH family of peptides which are derived from a larger precursor form (pro-opiomelano-cortin), synthesized in the brain and pituitary gland. Studies concern the mechanism of neurotransmitter signal transduction from the cell surface receptor to the nucleus to modulate specific gene expression and subsequent message translation, as well as the enzymology of post-translational modification of the pro-neuropeptide, which ultimately defines the peptide product secreted by the cell.

Laboratory of Molecular Genetics—
Igor Dawid, Ph.D.

Investigators in this laboratory use the tools of molecular and cellular biology to answer questions about gene transmission and recombination, and the regulation of genetic functions during development.

The range of model systems under investigation includes bacterial and animal viruses, transformed animal cells, yeasts, mouse and *Xenopus* embryos and the fruit fly *Drosophila melanogaster*. Recombinant DNA technology and gene transfer methods are emphasized. The development of novel vectors is being pursued for the introduction and expression of isolated genes in animal cells.

- Section on Developmental Biology—Igor Dawid, Ph.D.

Interest is focused on the molecular genetics of development. Gene expression during early embryonic stages of *Xenopus* is studied with the aid of cDNA libraries. Genes preferentially expressed during gastrulation are isolated with the aim of obtaining insight into the molecular events associated with the earliest stages of differentiation. Large regions of the *Drosophila* genome are being isolated using the technique of chromosomal walking so as to analyze the nature of developmental mutations. The organization of ribosomal RNA genes in *Drosophila* is also under study.

Methods are being developed to introduce cDNA copies of messenger RNA into mammalian cells in an expressible form. These methods are being used to search for cryptic oncogenes in transformed human cell lines. The regulation of amino acid biosynthesis is being studied in yeast. Regulatory genes and their products are being isolated and their interactions studied. The effects of *onc* gene mutations in yeast are also investigated.

- Section on Molecular Regulation—Michael Cashel, M.D., Ph.D.

The structure and regulation of activity of genes for ribosomal RNA in *E. coli* are studied using techniques that include *in vitro* mutagenesis and growth rate control by carbon source availability. Determinants for RNA processing and enzymes involved in this process are studied in bacteria and in animals. The functional characteristics of promoter and termination signals in ribosomal genes of *E. coli* are also under study, as is the secondary structure of ribosomal RNA and its role in processing reactions.

- Section on Microbial Genetics—Robert Weisberg, Ph.D.

Mechanisms of genetic recombination are studied using bacteriophage lambda. Experiments proceed at the level of genetics, nucleic acid structure, and enzymatic reactions. Studies are conducted to isolate and analyze host factors and the genes that are required for site-specific recombination, and work is carried out to elucidate the molecular mechanisms of the reactions catalyzed by these host factors.

- Section on Animal Viruses—Heiner Westphal, M.D.

This section studies the DNA-mediated transfer of isolated genes into mouse eggs, and their integration and expression during subsequent development. This work is being carried out with the aim of studying the regulation of expression of introduced genes in the intact animal. Another goal is to create mouse analogs of human genetic diseases by the transfer of "anti-sense" DNA. Other work in this section is concerned with the transcriptional regulation of adenovirus. Isolated viral genes and their products are injected into living cells as one aspect of these studies.

Laboratory of Developmental Pharmacology—
Daniel W. Nebert, M.D.

Research in this Laboratory has concentrated on attempts to understand drug-induced gene expression at the molecular level. This Laboratory studies mechanisms of enzyme regulation, with particular reference to the induction of drug-metabolizing enzymes by environmental chemicals as well as drugs. There is particular interest in relationships between the genetics of these enzyme systems and fundamental biological events such as teratogenesis, drug toxicity, carcinogenesis and mutagenesis. Other projects within the Laboratory employ the classical methods of clinical pharmacology and pharmacogenetics. One long-range goal is to design molecular biology-based assays to predict the individual risk in humans of drug-induced birth defects and chemically induced malignancies.

- Section on Pharmacogenetics and Molecular Teratology—
  Daniel W. Nebert, M.D.

Inbred strains of mice and cells in culture are probed with recombinant DNA and ancillary techniques to study the regulation and gene expression of drug-metabolizing enzymes with particular reference to the cytochrome P-450 system. Related research projects are in the areas of developmental biology, teratology, and the control of endogenous drug-metabolizing enzymes by hormones and other factors.

- Section on Regulation of Gene Expression—
  Howard J. Eisen, M.D.

This section examines the molecular mechanisms by which steroid hormones alter gene expression in target cells. Emphasis is on the use of genetic models of hormone- or drug-resistance to study the biochemical functions of receptor proteins, the development of methods for isolation and immunochemical characterization of receptors, and the rescue of genes that encode these receptors.

- Section on Drug Biotransformation—
  Ida S. Owens, Ph.D.

Investigations are directed toward Phase II drug metabolism, i.e., conjugation reactions in which enzymes (UDP glucuronosyltransferases) use as substrates bilirubin, endogenous steroids, or oxygenated drugs, carcinogens and other environmental pollutants. Mechanisms of gene expression and enzyme induction are explored via the use of immunochemical and recombinant DNA techniques, inbred strains of mice, and normal and mutant cells in culture. An additional goal is to understand the basis of, and to develop diagnostic or predictive molecular biology assays for, human genetic diseases involving variants of the Phase II enzymes.

Laboratory of Developmental and Molecular Immunity—
John Robbins, M.D.

The Laboratory conducts research into the developmental and molecular biology of "natural" and immunization-induced immunity to bacterial and other antigens. Emphasis has been placed on the study of pathogenic mechanisms, MHC and other antigenic molecules (including their purification and characterization), and on the immuno-regulatory mechanisms of the host. The hybridoma and recombinant DNA technologies, as well as the methods of macromolecular purification, have been applied to these problems.

- Section on Bacterial Disease Pathogenesis and Immunity—
  John Robbins, M.D.

A primary objective of this group has been to devise methods to increase the immunogenicity of the capsular polysaccharides of *H. influenzae* type b, pneumococci, and *E. coli* associated with invasive human diseases. Semisynthetic conjugates of these polysaccharides have been prepared which convert their immunogenic properties to those of T-cell dependence. These conjugates are also used to characterize the ontogeny and genetic control of the serum antibody response in humans. The physical-chemical characteristics of the pertussis toxin, and their relation to this molecule's toxin and protective activities, are also being studied. Monoclonal antibodies to the subunits of the toxin are being used as probes for the cloning of the gene(s) involved in its synthesis.

- Section on Immunoregulation and Cellular Control—
  Edgar Hanna, Ph.D.

Interest is focused on cellular, molecular, and genetic mechanisms involved in regulation of immune systems. Functional regulatory and effector T-cells are established as monoclonal lines. These lines are being phenotyped in order to map pathways of cell circuitry within immune systems.

- Section on Molecular Genetics of Immunity—
  Keiko Ozato, Ph.D.

Modification of transplantation antigen genes at the DNA level is undertaken in order to determine the structural basis for immunological polymorphism and the function of the gene products. Hybrid or mutant mouse H-2 genes are employed in the examination of serological polymorphism and T-cell recognition. Activation of paternal transplanta-

tion antigen genes is studied in developing embryos. The phenomenon of immunological unresponsiveness in pregnant females is explored at the level of molecular mechanisms.

Laboratory of Theoretical and Physical Biology—
David Rodbard, M.D.

This laboratory conducts a wide range of multidisciplinary and theoretical studies, applying mathematical, statistical, and computer-based techniques to the analysis of complex clinical, biological, biochemical and pharmacological problems. Experimental work in the laboratory involves the study of receptors for drugs, hormones and neurotransmitters; the pharmacokinetics of calcium, cortisol, glucose, carnitine, and amino acids in man; and the physical-chemical characterization of peptide hormones using polyacrylamide gel electrophoresis and related approaches.

- Section on Theoretical Biology—
  David Rodbard, M.D.

This section has been concerned with development of methods for characterization of complex receptor systems for drugs, hormones and neurotransmitters. The multiple enkephalin and benzodiazepine receptor systems are studied in the Laboratory as model systems. Refined computer analysis is used for mathematical modeling (simulation and curve fitting) to facilitate optimal experimental design and provide objective, quantitative interpretation of results. This section is also developing computer programs for applications in clinical investigation and practice, including computer adjustment of insulin dosage for persons with diabetes mellitus.

- Section on Macromolecular Analysis—
  Andreas Chrambach, Ph.D.

This section is concerned with the development of optimized methods and strategy for analytical and preparative gel electrophoretic methods, including steady-state 2-dimensional protein maps. The section's goal is to solve biologically important separation and isolation problems as applied to native macromolecules, subcellular particles and viruses. Recent applications include the characterization of insulin and glucocorticoid receptors, as well as plasma renin, and the development of gram-preparative methods for human growth hormone produced by recombinant DNA technology.

- Section on Metabolic Analysis and Mass Spectroscopy—
  Alfred L. Yergey, Ph.D.

This unit develops novel techniques in mass spectrometry to permit high sensitivity studies of neurotransmitters, steroids, amino acids, and metals such as calcium. Stable (non-radioactive) isotope tracers are employed to investigate the kinetics of metabolism of these species in man, and the time course of serum concentrations of these isotopes is measured by mass spectrometry and analyzed using computer models of compartmental distribution.

Endocrinology and Reproduction Research Branch—
Kevin J. Catt, M.D., Ph.D.

Current research is focused on the mechanisms controlling hormone secretion and action, with particular reference to hypothalamic-pituitary hormones and their receptor-mediated responses in endocrine target cells. This work includes the analysis of structure-function relationships displayed by peptide and glycoprotein hormones, and studies on the receptors and actions of hypothalamic peptides (GnRH, somatostatin, CRF, GRF), angiotensin II, ACTH, prolactin, and gonadotropins. The characterization and isolation of peptide hormone receptors, clarification of plasma-membrane related second messenger systems, and the elucidation of the control of steroidogenesis and glycogen synthesis, are major goals of the branch research program.

- Section on Hormonal Regulation—
  Kevin J. Catt, M.D., Ph.D.

Receptor-mediated aspects of peptide hormone action are studied in target tissues regulated by hypothalamic peptides, angiotensin II, and gonadotropins. The mechanisms of peptide hormone action are investigated in isolated pituitary cells (GnRH, CRF, GRF, somatostatin, angiotensin II), adrenal cells (ACTH, angiotensin II), and steroido-

genic cells of the testis and ovary (LH, FSH, prolactin, GnRH). In these target cells, the roles of cyclic nucleotides, calcium-dependent processes, and phospholipid turnover, are studied in relation to the control of cellular activity by the regulatory hormones.

- Section on Molecular Endocrinology—
  Maria Dufau, M.D., Ph.D.

This group investigates the molecular basis of peptide hormone action, with particular emphasis on the control of gonadal function; analyzes the nature of gonadotropin receptors and activation of steroid biosynthesis in testis and ovary; and investigates the properties and biological activity of circulating gonadotropins in physiologic regulation and clinical disorders of pituitary and gonadal function.

- Section on Molecular Structure and Protein Chemistry—
  Hao-Chia Chen, Ph.D.

Research is conducted in the area of structural analysis, chemical synthesis, and modification of molecules important to reproductive and developmental biology. Major emphasis is placed upon the elucidation of structural requirements for biological activities, e.g., agonism or antagonism of hypothalamic, pituitary and placental hormones. The effect of divalency of polypeptide hormones on their biological activities, as well as the design of synthetic antigens for the development of immunological assays and detection of gene products, are also under investigation.

- Section on Adrenal Cell Biology—
  Charles A. Strott, M.D.

Research is performed on the hormonal and molecular events responsible for adrenal steroid biosynthesis and secretion in mammals, using the comparative approach. Current studies include the identification and purification of specific steroid-binding proteins in the adrenal cortex, the role of the cytoskeleton in steroidogenesis, lipoprotein receptor activity, cholesterol metabolism, and the differential structure and function of the zones within the adrenal cortex.

- Section on Metabolic Regulation—
  Kuo-Ping Huang, Ph.D.

This group studies the hormonal regulation of glycogen metabolism as a model for determining the complex elements of multiple-site phosphorylation and dephosphorylation in the regulation of rate-limiting enzymes. The section also investigates the mechanisms of action of hormones which affect glycogen metabolism, both in normal tissues and in tissues from diabetic animals. A major effort is devoted to studies on protein kinase C, a key enzyme in the "signal transduction" pathway.

Cell Biology and Metabolism Branch—
Richard D. Klausner, M.D.

Research in this Branch is directed toward clarifying developmental aspects of intracellular structure and function. Various methods are being utilized to study receptor biosynthesis, dynamics, regulation, and degradation, using the human transferrin receptor as a model. The Branch also conducts clinical research on the fundamental mechanisms and treatment of patients with genetic disorders of iron metabolism (hemochromatosis) to learn how the intracellular traffic of iron is normally controlled, and at what level iron metabolism is abnormally regulated in such patients. In another area of interest, the Branch examines mechanisms by which intracellular architecture is maintained, providing the basis for the function and dynamics of cellular organelles.

- Section on Organelle and Receptor Structure and Function—
  Richard D. Klausner, M.D.

The human transferrin receptor is employed as a model for studying receptor dynamics and regulation. Moreover, the section explores how the cell controls biosynthesis of this receptor, as well as its inactivation or sequestration. Recombinant DNA and monoclonal antibody methods are adapted to these studies, as well as the explication of specific biochemical signals that determine the physical routing of receptors within cells. Membrane signal transduction is examined using the T cell antigen receptor and the interleukin-2 receptor in lymphocytes, and the coupling between receptor-ligand binding, kinase activation and phospho-

lipid metabolism is also studied. In other work, the section investigates the determinants of intracellular architecture in order to clarify the basis for the function and structure of various cellular organelles, e.g., the Golgi apparatus and microtubules.

National Institute of Dental Research

Harold Loe, D.D.S., Dr. Odont.
Director
Abner L. Notkins, M.D.
Director, Intramural Research
Bruce J. Baum, D.M.D., Ph.D.,
Clinical Director

The National Institute of Dental Research recruits about two or three dental and one or two medical staff fellows each year. Initial assignments are for 2 years and may be extended for a third year. Appointments for medical staff fellows usually begin on July 1 and for dental staff fellows on August 1. Selection of candidates is based on program needs and qualifications of candidates. The chiefs of branches and sections screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research positions will be made following personal interviews by chiefs of laboratories and branches who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chiefs are listed below. A brief sketch of the clinical research areas is provided. Prospective applicants desiring more information should write to Abner L. Notkins, M.D., Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, MD 20892.

Dental Staff Fellows

Dental staff fellows spend much of their first year (about two-thirds) providing a wide range of care for patients at the Clinical Center. The remaining time is spent in clinical or laboratory research. The second (and third) year will be spent primarily (about 80 percent) engaged in supervised research with some clinical care responsibilities. Dental staff fellows must have a dental licensure in the United States, a minimum of 1 year hospital dental experience, and a desire for a career in academic dentistry.

Medical Staff Fellows

The medical staff fellow is assigned to one of the clinical research programs within which he or she carries out both clinical and laboratory studies. In addition, the medical staff fellow is responsible for performing medical evaluation and followup of patients accepted under one of the Institute's research protocols. Medical staff fellows may also be assigned to one of the basic research laboratories where they devote all their time to participating in laboratory research. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIDR programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Clinical Research Branches

Diagnostic Systems Branch—
Richard L. Webber, D.D.S., Ph.D.

Investigations are directed toward research and development of diagnostic techniques. Specific emphasis is placed on radiologic and other noninvasive analysis techniques. The main focus is on interdisciplinary investigations linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement, and new geometric bases for quantitative analysis of tissue morphology.

Neurobiology and Anesthesiology Branch—

- Clinical Pain Section
  Ronald Dubner, D.D.S., Ph.D., Chief
  Mitchell Max, M.D., Clinical Coordinator

This group conducts research on neural, neuroendocrine, and psychological mechanisms of pain and pain relief in patients with a variety of acute and chronic pain syndromes: post-herpetic neuralgia, diabetic neuropathy, low back pain, myofacial pain-dysfunction, cancer and post-operative pain. Studies are underway to characterize the mechanism of action of opioid peptide release in patients undergoing oral surgery and its correlation with stress and pain; of serotonergic and noradrenergic drugs in patients with post-herpetic neuralgia; of periventricular electrical stimulation in patients with chronic benign pain; and of enkephalin analogues in cancer patients tolerant to morphine. Fellows will acquire experience in the design of analgesic studies, in the use of experimental pain models in humans, in the assessment of pain in humans, in the correlation of pain report and neurochemical mediators in acute and chronic pain conditions, and in clinical pain consultation.

National Caries Program: Epidemiology and Oral Disease Prevention Program—
James P. Carlos, D.D.S., M.P.H.

- Biometry Section—
  Janet Brunelle, M.S.
- Field Studies Section—
  James P. Carlos, D.D.S., M.P.H., Acting
- Microbial Systematics Section—
  Micah I. Krichevsky, Ph.D.
- Clinical Trials Section—
  Herschel Horowitz, D.D.S., M.P.H.
- Laboratory Methods Section—
  Horace M. Stiles, D.D.S., M.P.H., Ph.D.

This program conducts clinical, field and related studies concerned with the etiology, distribution and prevention of oral diseases. Epidemiologic methodology is employed to investigate such disorders as caries, periodontal diseases and orofacial malformations. Studies utilize broad representative population groups as well as communities with an unusual prevalence of disease conditions. Methods to enhance the effectiveness of fluorides are explored. Clinical trials of caries preventive agents and research into improved methods of analyzing data are conducted.

Clinical Investigation and Patient Care Branch—
Bruce J. Baum, D.M.D., Ph.D.

- Clinical Investigations Section—
  Bruce J. Baum, D.M.D., Ph.D.
- Patient Care Section—
  Michael W. Roberts, D.D.S., M.S.D.

This branch conducts laboratory and clinical studies on membrane control mechanisms of cell function. Particular

emphasis is focused on salivary gland cells. Laboratory investigations are carried out on signal transduction events, protein processing and translocation, and water and electrolyte secretion. The primary clinical studies are on the diagnosis and management of patients with salivary gland dysfunction. Attention is paid to salivary secretion, gustatory function and oral motor performance.

Basic Research Laboratories

Laboratory of Oral Biology and Physiology—
Arthur R. Hand, D.D.S.
- Experimental Morphology Section—
  Arthur R. Hand, D.D.S.
- Enzyme Chemistry Section—
  John E. Folk, Ph.D.

The laboratory conducts basic research on the structure and function of oral tissues, and on the posttranslational modification of proteins. Major emphasis is placed on elucidation of basic mechanisms of cellular secretion. Topics of current studies in this area include the role of the Golgi apparatus in protein transport and packaging; endocytic mechanisms, lysosomal function, and membrane dynamics; structure and function of intercellular junctions; cellular mechanisms regulating gene expression, protein synthesis, and exocytosis; and cell surface receptor localization in salivary glands. Studies of proteins and enzymes are aimed at elucidating their mechanisms of action and biological significance. Particular emphasis is placed on transglutaminases, enzymes which catalyze covalent crosslink formation, and a eukaryotic initiation factor which contains an unusual amino acid formed posttranslationally.

Bone Research Branch—
John D. Termine, Ph.D.
- Bone Cell Biology Section—
  A. H. Reddi, Ph.D.
- Proteoglycan Chemistry Section—
  Vincent C. Hascall, Ph.D.
- Skeletal Biophysics Section—
  Edward D. Eanes, Ph.D.
- Skeletal Biology Section—
  John D. Termine, Ph.D.

The Bone Research Branch studies the structure, development, biosynthesis and regulation of bones, teeth and cartilaginous tissues. Emphasis is given to studies of acquired and heritable disorders of the skeleton. Branch scientific disciplines encompass cell biology, molecular biology, protein and carbohydrate biochemistry, immunochemistry and molecular biophysics. Areas of study include: bone and cartilage cell biology; skeletal stem cell differentiation; regulation of skeletal tissue metabolism; structure and function of matrix macromolecules such as collagen, the proteoglycans and osteonectin; organization and structure of connective tissue using nuclear magnetic resonance spectroscopy; physical chemical characterization of hard tissue minerals and synthetic mineral formation systems; and mechanisms of bone formation in physiological models of fracture healing.

Laboratory of Developmental Biology and Anomalies—
George R. Martin, Ph.D.

Research is directed toward the elucidation of teratogen-induced and inherited malformations. Projects include studying molecular mechanisms of cellular development, migration, and tissue formation and interaction. Drugs are used to probe these steps. Alterations in the production of such macromolecules as glycoproteins, collagen, and proteoglycans are also studied. Studies are under way on the regulation of gene activity using recombinant DNA technology. Our emphasis is on normal, mutant, fetal, and malignant cells from bone, cartilage, and other connective tissues. Medical staff fellows in this laboratory are encouraged to pioneer new research areas.

Laboratory of Microbiology and Immunology—
Stephan E. Mergenhagen, Ph.D.
- Microbiology Section—
  Charles L. Wittenberger, Ph.D.
- Cellular Immunology Section—
  Sharon M. Wahl, Ph.D.
- Humoral Immunity Section—
  Ann L. Sandberg, Ph.D.
- Clinical Immunology Section—
  Reuben P. Siraganian, M.D., Ph.D.

Research in microbiology focuses on bacterial ecology and pathogenesis, regulatory mechanisms in the metabolism of carbohydrates by oral bacteria, and on the use of molecular biological techniques for studying the pathogenic potential of oral microorganisms. The immunology programs consist of studies on the purification and properties of lymphokines and monokines which are involved in the induction of immunity and inflammation, the regulation of connective tissue metabolism by lymphocytes and macrophages, and the biochemistry of immediate hypersensitivity reactions. While a dental or medical staff fellow is assigned to one of the sections and will work under a senior investigator, considerable opportunity exists for collaboration with scientists in other components of the laboratory.

Laboratory of Oral Medicine—
Abner Louis Notkins, M.D.

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology, and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (e.g., herpes simplex), with emphasis on recombinant DNA technology; the etiology and pathogenesis of leukoplakia and papillomas of the oral cavity; virus-induced immunopathology; the application of monoclonal antibody techniques to isolate viral variants; the influence of viral receptors in determining susceptibility to infection; the role of interferon in autoimmune diseases; the etiology of various dermatologic disorders including apthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (e.g., Sjogren's syndrome and salivary gland tumors) and endocrine glands (e.g., diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various drugs in the treatment of oral lesions.

Neurobiology and Anesthesiology Branch—
Ronald Dubner, D.D.S., Ph.D.

- Neural Mechanisms Section
  Ronald Dubner, D.D.S., Ph.D.

Research on peripheral and central nervous system mechanisms of oral-facial sensation is performed by this laboratory. In one major series of studies, behavioral responses in monkeys trained in pain and temperature discrimination tasks are correlated with single-cell neuronal activity recorded in the medullary dorsal horn, thalamus and cerebral cortex. Correlative electrophysiological and morphological studies examine the characteristics of single cells in the dorsal horn and relate their function to morphology and neuronal circuitry. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions.

Other studies are examining the effects of nerve damage on neuro-chemical mediators in the dorsal horn utilizing radioimmunoassay, immunocytochemistry and molecular biology approaches. In addition, electro-physiological methods are used to examine changes in dorsal horn neuronal activity following such nerve lesions.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D.,
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biologic factors in the environment that can adversely affect man, to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents, and to provide

the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within man on the susceptibility to and course of disease induced by these agents.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 11 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Medical Staff Fellows

Medical staff fellows work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each fellow will work directly under a senior scientist in an area of research chosen by the fellow and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, medical staff fellows may work out informal arrangements with the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIEHS programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Intramural Research Laboratories

Laboratory of Pharmacology—
John R. Bend, Ph.D.

The toxic effects of low-level and/or chronic exposure to environmental constituents or contaminants on mammals and marine species are studied in this laboratory. Interactions (on or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently under way include: toxication-detoxication systems in the liver, lung, and skin and effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in the lung and liver; species differences in xenobiotic disposition and metabolism; and studies on the formation and metabolism of reactive metabolites of hydrocarbons in various marine species and purification and comparison of components of toxication-detoxication systems in various organs.

Laboratory of Reproductive and Developmental Toxicology—
John A. McLachlan, Ph.D.

Scientific efforts are directed toward the understanding of mechanisms of tox-

icity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis with *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratology potential; study the molecular mechanisms underlying cellular differentiation; evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects that do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of toxicity with the use of *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—
Donald I. McRee, Ph.D.

Research is concerned with the study of changes in behavior and neurologic function produced by long-term exposure to low levels of many chemical and physical agents present in the environment. Special consideration is being given to the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanisms whereby environmental factors produce behavioral and neurotoxic effects, and studies concerning the conditions that predispose individuals to the behavioral and neurotoxic effects of environmental factors.

Laboratory of Pulmonary Pathobiology—
Paul Nettesheim, M.D.

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Laboratory of Molecular Biophysics—
Colin F. Chignell, Ph.D.

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high-pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials, and their metabolites emphasize biomechanism elucidation.

Laboratory of Genetics—
Burke Judd, Ph.D.

This laboratory concentrates on studies on the genetic structure of populations and on the structural and functional organization of higher eukaryotic genes, using model systems such as *Drosophila* and cultured mammalian cells. A group in genetic enzymology seeks to develop rapid and efficient methods for the purification of specific macromolecules, proteins, and nucleic acids. One project in chemical genetics focuses on the analysis of mutant mammalian proteins and DNA using primary sequence analysis.

Biometry and Risk Assessment Program—
David G. Hoel, Ph.D.

The Biometry and Risk Assessment Program conducts basic and applied environmental health-oriented research in the areas of risk assessment, statistics,

biomathematics, and epidemiology. In addition it assumes responsibility for data management and statistical analysis in the Toxicology Research and Testing Program, and provides statistical, mathematical, data processing, and computer engineering support to the other programs of the Institute. Organizationally, the program is divided into a Statistics and Biomathematics Branch, an Epidemiology Branch, and a Computer Technology Branch.

Statistics and Biomathematics Branch—

The Statistics and Biomathematics Branch conducts a broad research effort ranging from statistical analysis to biomathematical modeling aimed at developing new or improved methods for quantitative risk estimation, particularly in the areas of carcinogenesis, mutagenesis, and reproduction. Branch scientists also maintain an active research program in statistical methodology relevant to design and analysis issues arising in laboratory experimentation with special emphasis on toxicological screening assays.

Epidemiology Branch—

The Epidemiology Branch initiates field studies of human disease, particularly chronic disease, due to environmental pollutants. The branch also investigates the effects of environmental toxins on fetal and child development and conducts basic and applied research in laboratory support methodology involved in the monitoring of human populations.

Computer Technology Branch—
Thomas A. Clemmer, M.S.

The Computer Technology Branch operates the Institute's computer systems and provides programming consultation services, including software systems development, to Institute personnel. It also maintains an active computer engineering group and furnishes systems analysis and project management support to various groups throughout the Institute.

Toxicology Research and Testing Program—
Ernest E. McConnell, D.V.M.
Acting

The Toxicology Research and Testing Program—the NIH operating component of the National Toxicology Program—develops, validates, and evaluates methods for toxicity testing of chemicals and other environmental agents; is responsible for toxicity testing, using both short- and long-term bioassays, to determine or ascertain toxicity of chemicals and other environmental agents; coordinates and communicates test development and testing program with other government agencies; and disseminates results of research, testing, methods development, and validation efforts to the scientific and public communities and to the regulatory agencies.

National Institute of General Medical Sciences

Ruth L. Kirschstein, M.D.
Director
Christine K. Carrico, Ph.D.
Director, Pharmacology Research Associate Program

Pharmacology Research Associates

The National Institute of General Medical Sciences (NIGMS) has 11 positions (medical staff fellow and staff fellow) available each year for pharmacology research training. The Pharmacology Research Associate Program seeks to

develop leaders in pharmacological research for key positions in academic, industrial, and Federal research laboratories. It is intended for those who have made a commitment to pharmacology in their training or research, and for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in the field of pharmacology.

Those who are appointed begin on July 1 and receive 2 years of postdoctoral training in one of the participating laboratories of the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Fellows engage in research relating the principles of pharmacological sciences to contemporary biomedical problems. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, biophysics, and instrumentation is also available. During their tenure, pharmacology research fellows devote the major portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities. A variety of laboratory problems and different research approaches advance both the work in progress and the competence of the prospective independent investigator.

Professional growth is stimulated through personal guidance by outstanding senior NIH and ADAMHA scientists who serve as preceptors. Preceptors and research fellows are matched by a mutual selection process after personal interviews.

Candidates for pharmacology research associate positions include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience or training in areas relevant to pharmacology. Those with research experience in a related area who wish to further their development in pharmacology are also eligible. Applicants with the M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related discipline.

Program Areas

The choice of a specific laboratory depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request any senior NIH or ADAMHA scientist as a preceptor. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities.

Clinical Pharmacology

Clinical pharmacology is an evolving research discipline that addresses the need for investigators to carry out pharmacological studies that relate to the mechanism(s) of action of clinically relevant drugs. An opportunity is available for 2 years of research training specifically in an area of clinical pharmacology. Applicants for this training should have the M.D. degree and a minimum of 1 year, preferably 2, of graduate medical training (internship or residency). This is a particularly good opportunity for M.D.'s who have not had extensive independent laboratory experience but who are committed to obtaining such experience. For this reason, an intensive laboratory experience in at least one of the programs described in the next section constitutes 50 to 75 percent of the clinical pharmacology program. In order to prepare fellows either to relate laboratory methods to studies in humans or to carry out mechanistically oriented studies in humans, the program also includes training in such general clinical pharmacological principles as pharmacokinetics, pharmacodynamics, biostatistics, and drug evaluation.

In addition to the listed laboratory preceptors, investigators who are actively engaged in clinical pharmacological research in the Warren Grant Magnuson Clinical Center, NIH, are available to

address fellows' special areas of need on an individualized basis. These preceptors include but are not limited to:

James R. Gillette, Ph.D., Chief, Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute

Harry Keiser, M.D., Clinical Director, National Heart, Lung, and Blood Institute

Charles Myers, M.D., Chief, Clinical Pharmacology Branch, National Cancer Institute

Daniel W. Nebert, M.D., Chief, Laboratory of Developmental Pharmacology, National Institute of Child Health and Human Development

Snorri S. Thorgeirsson, M.D., Ph.D., Chief, Laboratory of Experimental Carcinogenesis, National Cancer Institute

Markku Linnoila, M.D., Ph.D., Chief, Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism

William Z. Potter, M.D., Ph.D., intramural clinical pharmacologist, serves as coordinator of each fellow's overall training in clinical pharmacology. The clinical pharmacology fellows' research experiences are planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience can involve both laboratory and human investigation.

A training plan, including formal coursework, is developed for each fellow. A series of seminars are organized with the participation of the clinical pharmacology fellows to ensure that their needs are met.

An applicant may be considered for both the regular pharmacology research associate program and the clinical pharmacology option. Further information may be obtained from the Pharmacology Research Associate Program, NIGMS, NIH, Westwood Building, Room 919, Bethesda, Maryland 20892 (301/496-7707).

National Cancer Institute

Laboratory of Molecular Biology

Ira Pastan, M.D.

This laboratory is interested in developing immunotoxins for the treatment of human cancer. To accomplish this, *Pseudomonas* exotoxin is coupled to monoclonal antibodies that react with specific human cancers. The activity of these conjugates is assessed in cell culture and in animal models. Toxicity studies are currently being carried out in monkeys with the first promising immunotoxins in preparation for clinical testing. The mechanisms by which immunotoxins enter and kill cells is studied by biochemical, genetic, and cell biological approaches in order to devise ways to improve the therapeutic efficiency of these agents.

- Molecular Cell Genetics Section—Michael M. Gottesman, M.D.

This section develops tissue culture genetic models for the analysis of the mechanism(s) of drug resistance in human cancer cells. The scientists' work has emphasized the establishment of human cell lines resistant to multiple drugs with the aim of understanding the molecular basis of this resistance. Genetic studies include dominance analysis using somatic cell hybrids and techniques of DNA-mediated gene transfer to clone mutant or amplified genes involved in the multiple-drug-resistance phenotype. Biochemical studies include use of monoclonal antibodies to study cell-surface alterations in resistant cells and studies on uptake of drugs by resistant cells. Other research focuses on resistance of cell lines to anti-microtubule agents due to alterations in α- and β-tubulins and the role of cyclic AMP in regulating cell growth.

Laboratory of Mathematical Biology

- Pharmacology of Biologicals Program

John N. Weinstein, M.D., Ph.D.

The principal aim of this group is to understand the pharmacology of biological agents. As it becomes increasingly feasible to tailor biologicals to order, the lack of information on their pharmacology remains a major barrier to rational design. The group is taking a combined experimental/theoretical approach to the question, with current emphasis on monoclonal antibodies. Experiments are being done at several levels, ranging from detailed analyses of antibody binding and cell biology to whole-animal biodistribution studies. Also included is a program on immunotoxins and other effectors aimed at tumor cell killing and immune modulation. All of the *in vitro* and animal studies are closely correlated with clinical protocols on which members of the group are working.

On the theoretical side, the group is constructing both compartmental and distributed models using data from animal and human studies. Concepts arising from the models are then used to refine or redesign the protocols and also the biological agents themselves. A current focus is the delivery of antibodies via lymphatic vessels (rather than the bloodstream) for the diagnosis and therapy of lymphoma and metastatic solid tumors in lymph nodes.

Metabolism Branch

- Endocrinology Section—

James M. Phang, M.D.

This research program emphasizes the functions of metabolic intermediates as regulatory molecules and the modulation of these functions by hormones. Of special interest is pyrroline-5-carboxylate, the obligate intermediate in the interconversions of proline, ornithine, and glutamate. This molecule serves as a metabolic interlink between amino acids and ribonucleotides and participates in the early cellular events accompanying mitogenic activation by growth factors. Pyrroline-5-carboxylate also acts as an intercellular communicator. It is found in biological fluids such as plasma and aqueous humor and functions to transfer metabolic signals between cells and tissues.

Several approaches are used to elucidate the mechanisms of the pyrroline-5-carboxylate metabolic interlink and to demonstrate its physiologic significance. These include cellular physiology, biochemistry, molecular biology, and human physiology. This group is studying the processing of these signals to regulate ribonucleotide metabolism and gene expression. The investigators are also characterizing the enzymes of this regulatory system and planning to clone the genes coding for these enzymes. With the understanding of these mechanisms in normal and malignant cells, the scientists will seek specific pharmacologic approaches in order to manipulate pyrroline-5-carboxylate-mediated cellular response in normal and neoplastic cells.

Laboratory of Tumor Virus Biology

Peter M. Howley, M.D.

This laboratory engages in several areas of research to determine critical cellular and molecular factors involved in virus-associated transformation. Studies are designed to: (1) identify and characterize exogenous viruses associated with the initiation or progression of neoplasia in humans or in animals as models for human neoplasia; (2) elucidate the mechanisms by which viruses associated with naturally occurring carcinomas may induce or initiate neoplasia; (3) characterize and define the biology and molecular biology of viruses associated with naturally occurring carcinomas; (4) identify and characterize factors involved in viral and cellular gene regulation pertinent to carcinogenesis; and (5) elucidate and define the cellular and molecular basis of transformation and carcinogenic progression.

The major research effort of the laboratory is focused on the molecular biology of the papillomaviruses, including transcriptional regulation, transformation, plasmid replication, and carcinogenesis. The laboratory has also been involved in developing the papillomaviruses as mammalian cell cloning vectors and is interested in using these vectors to study

regulated genes such as the human β-interferon gene and the rat pre-proinsulin gene. These studies are designed to determine the genetic sequences involved in proper gene regulation and to isolate cellular protein factors required for this regulation.

Laboratory of Experimental Carcinogenesis

Snorri S. Thorgeirsson, M.D., Ph.D.

This laboratory plans, develops, and implements a research program to elucidate mechanisms of malignant transformation in human and animal cells by chemical carcinogens and other cancer-causing agents; determines critical cellular and genetic factors involved in the initiation, promotion, and progression of these transformed cells; and, whenever possible, applies the knowledge obtained from these studies toward the effective prevention of cancer in humans. Studies are designed to: (1) identify and characterize exogenous and endogenous factors controlling the initiation, promotion, and progression of chemically induced tumors; (2) elucidate the mechanisms underlying the regulation of gene expression and differentiation in both human and animal neoplasia; (3) define the mechanism by which modifiers of cellular differentiation may inhibit and/or promote the neoplastic process; and (4) characterize the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines.

Laboratory of Experimental Carcinogenesis

- Hormone Action and Oncogenesis Section—

  Gordon L. Hager, Ph.D.

This laboratory's central program concerns the mechanism of gene regulation in eukaryotic cells, particularly with regard to steroid hormone molulation of gene activity. The researchers utilize the mouse mammary tumor virus (MMTV) system, which is responsive to glucocorticoid regulation. This model promoter has been mobilized on high-copy, stable, episomal vectors in cultured cells to permit a detailed analysis of hormone action at the chromatin level. The laboratory is also involved in the development of vectors for the efficient transmission of genes under expression control, both for basic investigations and in medical applications. These vectors are retrovirus-based and utilize hormone-regulated promoters to permit control of expression after gene transmission. It is expected that control of gene activity will become a central issue in gene therapy protocols. Finally, the group is interested in mechanisms of oncogenesis, specifically in the function of the ras oncogene and in the mechanisms of MMTV-induced mammary cancer.

Laboratory of Human Carcinogenesis

Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess: (1) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, (2) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation, and (3) host factors that determine differences in carcinogenic susceptibility among individuals. The three major areas of investigation are: *Molecular and Biochemical Epidemiology* focuses on measurement of gene polymorphismn by molecular approaches (*e.g.,* DNA polymorphism) to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens. *Carcinogen Macromolecular Interaction* involves studies of the activation of cellular oncogenes by carcinogens; identification of metabolic pathways of carcinogen activation and deactivation; inter- and intragenic damage and rearrangements caused by chemical and physical carcinogens; and determination of the importance of repair of carcinogen-induced damage to DNA and chromosomes in carcinogenesis. *In Vitro Carcinogenesis* investigates the mechanisms of neoplastic trans-

formation; the role of oncogenes in human cell carcinogenesis; phenotypic and genetic alterations during *in vitro* carcinogenesis; the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and extra-, inter-, and intracellular factors modulating growth and differentiation of human epithelial cells.

Laboratory of Cellular Carcinogenesis and Tumor Promotion

- Molecular Mechanisms of Tumor Promotion Section—
  Peter M. Blumberg, Ph.D.

Tumor promoters are agents which, although not themselves carcinogenic, induce tumors in animals previously exposed to a sub-effective dose of a carcinogen. This section is studying the mechanism of action of the most potent class of tumor promoters for mouse skin, the phorbol esters, and has demonstrated that cells and tissues contain specific phorbol ester receptors. Characterization indicates that the major class of these receptors is identical to protein kinase C, to which the phorbol esters bind at a modulatory site. Diacylglycerol, an activator of protein kinase C, appears to be the endogenous analog of the phorbol esters, and the postulated normal role for the phorbol ester receptor/protein kinase C is to mediate responses to that large class of hormones and cellular effectors whose action is associated with phosphatidylinositol turnover rather than elevated cyclic AMP levels. Current research directions include clarifying the interactions of the receptor with membranes, determining the basis of receptor subclasses, defining the mechanism of coupling between phorbol ester binding and kinase activation, and tracing the pathways between substrate phosphorylation and subsequent biological response.

Laboratory of Pharmacology and Experimental Therapeutics

David G. Johns, M.D., Ph.D.

The laboratory is made up of three sections: Medicinal Chemistry, Molecular Toxicology, and Biochemical Pharmacology. The laboratory conducts an integrated program for the rational discovery of antitumor agents, and implements basic research on mechanisms of antitumor drug action and drug toxicity. It incorporates knowledge of biochemical and molecular mechanisms into a drug synthesis program aimed at optimizing drug efficacy through enhancement of antitumor activity/selectivity and/or minimization of toxicity, and develops strategies for improving the clinical utility of new or existing anticancer drugs by overcoming tumor resistance and/or by protection of normal tissues against toxicity. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites (*e.g.,* nucleic acids, nuclear proteins, microtubular protein, and enzyme systems). Analytical methodology is developed for *in vivo* studies with new agents and, where warranted, biological studies with these agents are extended to the prelinical and Phase I stages. At the present time, three agents synthesized and developed within the laboratory are in Phase I or II clinical trials, while a fourth agent is scheduled for a clinical trial within the next year. Other agents are under active study. A wide range of methodologies are currently in use, including soft agar cloning and other tissue culture techniques; instrumental analysis, with emphasis on mass spectrometry, electron microscopy, high pressure liquid chromatography, and affinity chromatography; DNA and RNA isolation and characterization; hybridization; autoradiography; pharmacokinetic analysis; and enzyme purification.

Laboratory of Experimental Therapeutics and Metabolism

Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is analytical and clinical pharmacology involving studies on qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents using experimental systems, as well as in a clinical setting. Problems are selected for their relevance to the

development and/or evaluation of new chemotherapy protocols, and frequently are pursued in collaboration with other NCI laboratories. The other major research area concerns the elucidation of fundamental chemicobiologic interactions underlying chemically-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest, as are investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites in both normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemically–induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimum toxicity to normal tissues.

Laboratory of Biological Chemistry
Richard L. Cysyk, Ph.D.

This laboratory brings together scientists who identify, as targets for drug design, cellular reactions that are critical to tumor cell survival and to the control of cell division and differentiation. Emphasis is placed on targets uncovered by recent advances in cell biology. Compounds are designed to interfere with these targets and are evaluated for biochemical and antitumor effectiveness. Pharmacologic information—plasma levels, tissue levels, mechanisms of action, transport, and metabolism—is used for experimental chemotherapy and for preclinical evaluation of an agent. An important aspect of the selective toxicity of an agent is the effect of endogenous factors present *in vivo* that can modify the cytotoxic properties of the agent and thereby influence differential toxicity. This laboratory identifies and quantitates such endogenous factors, when possible, and devises methods to manipulate them to enhance the chemotherapeutic effectiveness of cytotoxic compounds.

Laboratory of Biological Chemistry
Robert I. Glazer, Ph.D.

This laboratory conducts molecular studies of the mechanism of action of differentiating agents and anticancer drugs in human tumor cell lines in tissue culture. Areas currently receiving the greatest emphasis include cellular oncogene and protein kinase expression during cellular differentiation, as well as drug resistance. Current investigations include the effects of immune interferon, tumor necrosis factor, phorbol esters, and other differentiating agents on the induction and characterization of tyrosine and calcium-phospholipid protein kinase activities in HL-60 cells. The latter activities are also being characterized in human tumor lines showing pleiotropic drug resistance. A variety of immunologic and molecular techniques are employed in investigating the various facets of this problem.

Medicine Branch
Medical Breast Cancer Section
Marc E. Lippman, M.D.

The research program of this section deals with the mechanism of action of sex steroid hormones in human breast cancer. This problem has been approached from several directions. A variety of estrogen-regulated genes have been identified and cloned, and the basis of their control by estrogens and antiestrogens is being examined. A large number of hormone- and drug-independent mutants have been derived from wild-type cells and the molecular basis of hormone independence has been explored using biochemical and genetic approaches. Intracellular pathways of growth regulation of human breast cancer have also been explored by the introduction of exogenous genetic material in the form of oncogenes into human breast cancer cells and a delineation of their impact on growth control has been examined. In addition, the cell biology and molecular pharmacology of a variety of tagged monoclonal antibodies and novel estrogens are being explored as imaging agents and as cytotoxic therapeutic tools in cell culture, nude mice, and eventually in clinical studies.

Clinical Pharmacology Branch
Charles Myers, M.D.

This laboratory is involved in the biochemistry of adriamycin-iron complexes, including their free radical products. This process involves examination of how these complexes bind to and cleave DNA. In addition, studies are planned to assess the biologic role of these drug-metal complexes. The other major area in the laboratory revolves around the enzymatic defenses of mammalian cells against free radical attack. In the process, the investigators appear to have discovered a new family of peroxidases which they are in the process of purifying and characterizing. Projects are available investigating the role of these enzymes in the detoxification of drug-induced free radicals. State-of-the-art high-resolution NMR and ESR equipment is available in the branch and is currently being used to study the chemistry and three-dimensional structure of the interaction of adriamycin with DNA and other targets.

National Institute of Heart, Lung, and Blood

Hypertension-Endocrine Branch—

- Section on Biochemical Pharmacology—
  Ingeborg Hanbauer, Ph.D.

Work in this laboratory focuses on regulation of the release of catecholamines and enkephalin-like peptides fron adrenal glands. The effects of electrical stimulation of the splanchnic nerve, and those of specific agonists and antagonists of GABA-ergic nicotinic or opiate receptors, on the release of the met-enkephalin-like peptides epinephrine and norepinephrine are investigated. The peptides released from the adrenal chromaffin cells into the adrenal venous blood are characterized by high pressure liquid chromatography and radioimmunoassay using specific antibodies.

Ongoing work also focuses on pharmacologic and biochemical aspects of the regulation of striatal dopamine receptors. The regulation of dopamine receptors is studied in the corpus striatum, with particular attention on two functional states, sub- and supersensitivity. These studies comprise measurements of dopamine recognition sites, G/F protein, adenylate cyclase, calmodulin, and phosphorylation and dephosphorylation of membrane proteins and protein kinases. Furthermore, studies are carried out on the regulation of nitrendipine- and verapamil-sensitive Ca^{2+}channels in various brain areas. This work pursues the isolation and characterization of recognition sites for these ligands and of endogenous ligands acting on these recognition sites.

Laboratory of Biochemical Genetics
Marshall W. Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall W. Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry, particularly those that pertain to the development of the nervous system, are studied in this section. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Polyclonal and monoclonal antibodies are being used to detect protein whose expression is dependent on cloned DNA. Cultured cells are used in many studies. Research also is being conducted on cyclic nucleotides, receptors, and ion channels.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms in *Escherichia coli.* One area of interest concerns the control of the synthesis and metabolism of cyclic AMP in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells. The laboratory is using biochemical and recombinant DNA approaches to study the regulation of expression of the gene for adenylate cyclase as well as the factors that regulate the enzyme's activity. Another focus of attention is the

Escherichia coli cyclic AMP receptor protein. Analyses of structure, function, and repression mechanisms involving this protein are under way.

Laboratory of Chemical Pharmacology
James R. Gillette, Ph.D.

- Section on Drug-Enzyme Interaction—
  James R. Gillette, Ph.D.

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal levels.

Laboratory of Chemical Pharmacology

- Section on Cellular Pharmacology
  Michael A. Beaven, Ph.D.

This section studies drug action at the cellular level. Current work includes: studies on the mechanism of mast cell/-basophil degranulation, particularly on the interrelationship of signals generated by Ca^{2+} fluxes and breakdown of inositol phospholipids; studies with purified and cultured populations of cells from gastric mucosa and blood vessels to determine the biochemical responses to histamine and other active hormones; and research on the release and metabolism of histamine and other active factors during inflammatory and allergic reactions.

- Section on Pharmacological Chemistry—
  Lance R. Pohl, Pharm.D., Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identification of active substances formed in the body, the biochemical basis of their pharmacologic and toxicologic actions, and the characterization and regulation of the enzymes that either produce or metabolize these agents. This section is particularly interested in the mechanism of drug-induced autoimmune diseases. In addition, it is involved in the study of the mechanism and regulation of the turnover of cytochromes P-450 in the liver, adrenals, testes, and ovaries.

Laboratory of Molecular Hematology
W. French Anderson, M.D.

This laboratory studies the mechanism and regulation of mammalian gene expression, using hemoglobin biosynthesis as one of its primary models. The major objective is to develop the understanding and techniques necessary to carry out gene therapy for human genetic diseases. Major areas of research include: gene cloning and gene transfer, retroviral vector development, isolation and characterization of trans factors involved in gene expression, and drug-induced (5-azacytidine, hydroxyurea, cytosine arabinoside, etc.) alteration of globin gene expression by examination of the mechanism of action of these agents.

Laboratory of Cellular Metabolism
Martha Vaughan, M.D.

Using techniques of molecular genetics, biochemistry, and cell biology, this laboratory conducts research directed toward understanding the regulation of cyclic nucleotide synthesis and degradation. Cyclic AMP synthesis by the membrane-associated adenylate cyclase complex is controlled by stimulatory and inhibitory agonists (*e.g.*, hormones, drugs) acting through cell-surface receptors. Signals generated by receptor-agonist interaction are transmitted to the cyclase catalytic unit via GTP-binding coupling proteins, which are targets for covalent modification (ADP ribosylation) catalyzed by bacterial toxins (*e.g.*, cholera toxin, pertussis toxin) that activate the cyclase. Areas of current interest include: (1) molecular biology: isolation of cDNAs and genes for the regulatory components of adenylate cyclase, analysis of mRNA content and structure in differentiating systems, (2) membrane biochemistry: molecular mechanisms for the interaction of adenylate cyclase components (e.g., studies with site-specific monoclonal antibodies, reconstitution of purified proteins) and effects of toxin-

catalyzed ADP ribosylation on the interaction of coupling proteins with receptors and the cyclase catalytic unit; (3) cell biology: effects of hormones and toxins on cyclic nucleotide content of cultured cells; and (4) enzymology: identification of ADP ribosyltransferases and their substrates in animal cells, effects of ADP ribosylation on enzyme function, regulatory properties of the phosphodiesterases that degrade cyclic nucleotides, and mechanisms by which calmodulin modifies the activities of phosphodiesterase and other proteins with which it interacts.

Laboratory of Cell Biology
Edward D. Korn, Ph.D.

This laboratory's research is concerned with the regulation of the polymerization and enzymatic activity of actin and myosin, the two major cytoskeletal proteins of the membrane-cytoskeleton complex of non-muscle cells. The investigators are studying the ways in which ATP hydrolysis regulates actin polymerization and how myosin phosphorylation regulates myosin polymerization, actomyosin ATP-ase activity, and contractile activity. These studies include active site sequence determination and structure-function relationships studied through a variety of protein physical-chemical methods. Other research involves isolating and sequencing myosin genes, with plans to undertake site-directed mutagenesis to explore further the chemical basis of actin and myosin function. Also under investigation is the action of drugs such as cytochalasin D in order to understand at the molecular level their effects on the membrane-cytoskeleton complex.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Arthritis and Rheumatism Branch—

- Section on Chemical Immunology—
  Henry Metzger, M.D.

This section is studying mast cell secretion mediated by the high-affinity receptor for immunoglobulin E. The studies involve isolation, characterization, and reconstitution (into liposomes) of the receptor and exploration of biochemical perturbations during triggering. This system serves as a powerful model for examining at a molecular level the proximal events in cellular secretion mediated by a cell-surface receptor.

Genetics and Biochemistry Branch—
R. Daniel Camerini-Otero, M.D., Ph.D.

This laboratory studies the mechanisms of genetic recombination and gene conversion in mammalian cells, the regulation of gene expression in higher eukaryotes, and the biochemistry of nucleic acid-protein interactions. This group also conducts studies on the effects of physical and chemical agents on genetic recombination and DNA repair in mammalian cells. In several cases material from patients with genetic diseases is used to dissect the biochemical or molecular aspects of a problem under investigation. In order to carry out these studies the techniques utilized include molecular cloning, DNA sequencing, DNA-mediated gene transfer, construction of gene fusions and recombinant DNA libraries, and a variety of other biochemical and molecular techniques.

Digestive Diseases Branch—
Jerry D. Gardner, M.D.

This laboratory investigates the cellular basis of action of gastrointestinal peptides using various isolated cell systems prepared from different gastrointestinal tissues. Gastrointestinal peptides being studied are cholecystokinin, secretin, VIP, PHI, bombesin, physalaemin, substance P, ranatensin, galanin, pancreatic polypeptide, and calcitonin gene-related peptide. Isolated cell systems have been prepared for gastric chief cells, gastric parietal cells, pancreatic acinar cells, gastrointestinal smooth muscle cells, small intestinal epithelial cells, colonic epithelial cells, hepatic parenchymal cells, and hepatic Kupfer cells. Studies of the cellular basis of action of a particular peptide include receptor identification; development of receptor-specific antagonists; exploration of the intracellular

sequence of messenger action; and the relation among the final response, receptor occupation, and messenger variation.

Molecular, Cellular, and Nutritional Endocrinology Branch—

- Section on Experimental Diabetes, Metabolism, and Nutrition
  Samuel W. Cushman, Ph.D.

Insulin's fundamental action to stimulate glucose transport has recently been shown to occur in the rat adipose cell model system through a rapid and reversible exocytic-/endocytic-like subcellular cycling of glucose transporters between a large intracellular pool and the plasma membrane. Insulin also stimulates the appearance of cell-surface insulin-like growth factor II (IGF-II) receptors and concomitantly induces insulin receptor internalization through similar rapid and reversible membrane translocation processes. Using biochemical, cell biological, and immunologic laboratory techniques, the section: (1) investigates the structure, function, and biosynthesis of integral membrane proteins involved in the hormonal regulation of carbohydrate and lipid metabolism, especially the receptors for insulin and IGF-II and the glucose transporter; (2) studies the molecular and cellular basis of hormone action, especially relating to the mechanism of insulin action and its counterregulation by catecholamines, other peptide hormones, and the glucocorticoids; and (3) examines the influence of altered metabolic and nutritional states on cellular function and its regulation by hormones, especially those states associated with perturbed insulin action such as diabetes, obesity, and altered dietary carbohydrate and fat intake.

- Section on Growth and Development
  Matthew M. Rechler, M.D.

The laboratory uses approaches of molecular and cellular biology to define the role in normal and pathological cell growth of a family of polypeptides, the insulin-like growth factors (IGF), present in plasma and chemically related to insulin. IGF receptors, actions, carrier proteins, and the regulation of IGF gene expression are studied in appropriate model systems. The role of IGF-II in fetal growth and development, and in central nervous system function, are areas of current interest.

Clinical Endocrinology Branch
Jacob Robbins, M.D.

The laboratory is engaged in studies related to the thyroid gland and thyroid hormones. The subjects of greatest interest have been thyroglobulin and related iodoproteins, the plasma transport proteins for thyroid hormones, the mechanism of entry of thyroid hormones into target cells, the metabolism of the hormones in tissues, and, on a clinical level, the management of thyroid neoplasms. In recent years, fellows have worked on the monodeiodination reaction responsible for the conversion of thyroxine to the active hormone, triiodothyronine, in liver cells; on energy-dependent transport of triiodothyronine and thyroxine into hepatocytes and into skeletal muscle, employing whole-organ and cultured-cell systems; and on the effect of lithium ion in slowing the release of thyroid iodine and lithium's use as an adjuvant in treating thyroid carcinoma with radioiodine. A current interest within the laboratory is to employ a continuous cell line of rat myoblasts to study the transport, metabolism, and actions of thyroid hormones in relation to myoblast differentiation.

Clinical Endocrinology Branch—

- Section on Endocrine Biochemistry—
  Jan Wolff, M.D., Ph.D.

The laboratory investigates cytoskeletal (especially microtubule) interactions with cell membrane functions, particularly adenylate cyclase. This involves tubulin chemistry, regulation of microtubule polymerization by associated proteins, calcium/calmodulin, and charge-charge effects, as well as the mechanism of action of antimicrotubule drugs. The laboratory is also studying regulation of membrane-bound and soluble adenylate cyclases by hormones, calmodulin, bacterial toxins, guanine nucleotide binding proteins including tubulin, and phospholipids. The goal is to understand the reciprocal regulation of these two components.

As an outgrowth of this work, the laboratory is studying adenosine receptors and antagonists, the role of bacterial

adenylate cyclases as virulence factors (along with toxins), their mechanism of activation, and their method of entry into host cells.

Metabolic Diseases Branch

- Molecular Pathophysiology Section
  Allen M. Spiegel, M.D.

A family of guanine nucleotide binding proteins (G proteins) transduces signals across membranes by coupling receptors to effector enzymes. Distinct G proteins couple: (1) receptors for hormones and neurotransmitters that stimulate or inhibit cAMP formation; (2) rhodopsin, a photoreceptor, to a cGMP phosphodiesterase; and (3) receptors for agonists that stimulate phosphatidylinositol turnover. The Molecular Pathophysiology Section studies the structure and function of G proteins. G proteins that have been purified and used for the production of antibodies have proved useful for studies of G protein structure, for immunocytochemical studies, for regional localization of G protein in brain and for quantitation of G proteins as a function of cell differentiation. The laboratory studies states of altered target cell responsiveness for possible quantitative or qualitative changes in G proteins. Thus, a human genetic disorder characterized by generalized hormone resistance has been shown to result from a deficiency in the G protein linked to adeylate cyclase stimulation. The laboratory also searches for novel G proteins involved in membrane transduction. Such a protein has been identified in human neutrophils. In addition, cDNA probes are employed to study alterations in G protein structure and synthesis.

Diabetes Branch

Phillip Gorden, M.D.
Jesse Roth, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially for insulin and insulin-like growth factors. Current projects are focused on the role of receptors and receptor antibodies in disease states, genetic disorders of the insulin receptor (including molecular biology of the receptor), biosynthesis of receptor components, the role of receptors in hormone action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects examine insulin and insulin receptors in the central nervous system; the evolutionary and embryologic origins of insulin, ACTH, somatostatin, and other peptide messenger molecules; and the role of such moleculls in vertebrate embryos and in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

Laboratory of Biochemistry and Metabolism

William B. Jakoby, Ph.D.

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to their catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action of those enzymes catalyzing conjugation reactions with glutathione or adding sulfate or methyl groups. Currently, a natural inhibitor of methylation is being evaluated at both the enzyme and cell culture levels.

- Section on Enzymes and Cellular Biochemistry—
  Enrico Cabib, Ph.D.

The main interest of this laboratory lies in the molecular mechanisms of morphogenesis in eukaryotic cells. As model systems, the primary septum and the cell wall of the yeast, *Saccharomyces cerevisiae,* are currently investigated. The approach consists of studying the biosynthesis of the main structural materials—chitin for the primary septum and β (1→ 3) glucan for the cell wall—at the enzymological, subcellular, and cellular levels. Since these materials impart shape to cell structures, it is expected that the information gathered in this way will give insights into the control and mechanism of shape formation. Techniques used include purification and kinetics of enzymes; isolation of subcellular structures, especially plasma membranes; elec-

tron microscopy; isolation of appropriate mutants; preparation of antibodies against polysaccharide synthetases; and cloning of the pertinent genes. Because of their potential use as antifungal agents, special attention is paid to inhibitors of the polysaccharide synthetases and to their mechanism of action.

Laboratory of Cell Biology and Genetics

• Section on Cell Biology and Biochemistry—
Harvey B. Pollard, M.D., Ph.D.

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells using techniques of molecular biology, electron microscopy, electrophysiology, cell biology, and biochemistry. The researchers are particularly interested in secretory processes in chromaffin cells, islets of Langerhans, platelets, and synaptosomes. Critical problems now under investigation include how secretory vesicle assembly is regulated, how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membranes, and how the subsequent release of vesicle contents during exocytosis occurs. The approach of this laboratory is to search for special proteins and processes that could mediate such events.

Laboratory of Biochemical Pharmacology

Herbert Tabor, M.D.

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (*e.g.,* spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. These studies provide experience with a variety of techniques (enzyme characterization, bacteriophage methodology, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed on the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and yeast.

Other work includes studies on control mechanisms for other enzymes in bacteria and mammalian cell cultures, the mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability. Investigations are also carried out on developmental biology and organ regeneration in the rat and aim at identifying and isolating those genes that must be espressed to attain or maintain a particular state of cell differentiation.

• Section on the Genetics of Simple Eukaryotes
Reed B. Wickner, M.D.

This section is studying the genetic control of replication of a set of double-stranded RNAs found in virus-like particles in the simple eukaryote *Saccharomyces cerevisiae* (yeast). These double-stranded RNAs determine the "killer trait," the production of a toxin lethal to yeast not carrying the virus. The laboratory has found that replication of the double-stranded RNA genome involves a large number of chromosomal genes, several genes on the double-stranded RNA segments themselves, and a mitochodrial gene. These components show many complex functional interactions. Current work to examine the nature of these genes and the mechanisms of their interactions involves genetics, enzymology, pharmacology, molecular cloning, and molecular biology.

Laboratory of Analytical Chemistry

• Steroid Hormones Section
S. Stoney Simons, Jr., Ph.D.

The objective of this group is to define, on a molecular level, the biological properties of the receptors for steroid hormones. Major efforts are devoted to studying the activities of glucocorticoid receptor-steroid complexes up to, and including, their effects on gene transcription. Current investigations concern the biochemistry of covalent, affinity-labeled glucocorticoid receptor-steroid complexes; purification of the covalently labeled complexes; examination of factors determining agonist versus antagonist activity for various steroid

hormones in the same and different cell lines; and the nature of the biologically active nuclear binding site for receptor-steroid complexes. The experimental approaches include tissue culture, whole-cell bioassays, nucleic acid hybridization, affinity labeling, gel electrophoresis, binding to cloned DNA sequences, nuclear protein fractionation, and synthetic organic chemistry.

Laboratory of Chemistry

- Section on Medicinal Chemistry
  Kenner C. Rice, Ph.D.

The primary focus of this program is the chemistry of drugs which affect the central nervous system, as it pertains to study of these agents and physiologic functions of their recognition sites. The narcotics and their antagonists, phencyclidine (PCP), benzodiazepines, and non-nitrogenous CNS agents are of particular interest. Synthetic organic chemistry is a major and indispensible tool in the multidisciplinary approach utilized in these studies, which involve collaboration with biochemists, immunologists, and biochemical, neurochemical, and behavioral pharmacologists. An ongoing program aimed at the identification, purification, and elucidation of the structure and function of opiate receptor subpopulations in the overall modulation of the CNS requires the synthesis of new receptor ligands for several lines of investigation utilizing: (1) irreversible ligands specific for opiate receptor subpopulations; (2) high-specific-activity radiolabeled ligands for autoradiographic visualization of receptors; (3) conformationally restricted analogs of potent narcotics as topological probes; and (4) positron emission tomographic visualization of opiate receptor patterns in living brains. Similar studies of PCP recognition site(s), including efforts to identify a clinically useful antagonist of PCP, are in progress. A more classical medicinal chemical program currently in progress involves application of the recently developed NIH Opiate Total Synthesis for synthesis of previously inaccessible unnatural enantiomers of important opium derivatives with the goal of identifying new pharmacologic agents and effects of opiates not mediated through the stereospecific receptors.

Laboratory of Physical Biology
Richard J. Podolsky, Ph.D.

This laboratory is concerned with the contraction and regulatory mechanisms in muscle cells. The primary goal is to gain an understanding of the molecular basis of force generation and shortening in muscle fibers. Present projects include one- and two-dimensional X-ray diffraction studies of intact and simplified muscle fiber preparations, correlation of filament structure derived from X-ray data with that obtained by electron microscopy, high time resolution mechanochemical studies, and radiation inactivation analysis of the physiologic function of various structural proteins.

Laboratory of Chemical Physics

- Section on Macromolecular Biophysics
  William A. Eaton, M.D., Ph.D.

This section studies structure-function relationships in proteins using biophysical methods. A major interest is the investigation of hemoglobin S polymerization in purified solutions and in intact red blood cells. The overall aim of this research is to obtain a quantitative description of the pathophysiology of sickle-cell disease and to design strategies for developing a specific therapy. In addition to conventional biophysical methods, a number of special techniques are employed, including microspectrophotometry, laser photolysis, and light scattering for studying the kinetics and thermodynamics of polymerization in single red blood cells. Other projects in the section include the study of oxygen binding by normal hemoglobin using time-resolved absorption spectroscopy with nanosecond pulsed lasers and molecular dynamics calculations to stimulate the motions of the individual atoms during the binding process.

Laboratory of Molecular Biology

- Section on Physical Chemistry—
  Gary Felsenfeld, Ph.D.

This laboratory conducts research on the structure of DNA and chromatin within the eukaryotic nucleus, with particular emphasis on mechanisms of regulation of gene expression. Present

studies are concerned with the isolation and characterization of specific factors that bind to the regulatory regions of genes that are being expressed, with the goals of identifying their roles in the control of expression and understanding in detail the molecular basis of that control. The laboratory also conducts physicochemical studies of DNA and its complexes with nuclear proteins. The methods used include standard techniques of molecular biology such as DNA cloning and sequencing, *Xenopus* oocyte injection, and *in vitro* transcriptional assays, as well as physicochemical methods applied to the determination of macromolecular structure and the measurement of the nature and strength of interactions between biologically important molecules.

Laboratory of Chemical Biology
Alan N. Schechter, M.D.

The major interest of this laboratory is understanding the control of differentiation and development of human erythroid cells, using cell biological and molecular genetic methods to study the control of globin gene expression. Cloned globin genes, including control regions, are being transfected into erythroid and non-erythroid eukaryotic cells in order to understand the DNA sequence-specific and intracellular soluble factors that control the sequential expression of these genes. This work has as one of its long-range goals the possibility of treating human genetic diseases by transferring new genes into cells of patients. In addition to these basic studies, clinical protocols are under way to use noninvasive modalities (*e.g.*, NMR imaging) to evaluate disease severity and response to therapy in sickle-cell patients and to use drugs (*e.g.*, hydroxyurea) to activate fetal hemoglobin genes in patients with hemoglobinopathies.

Laboratory on Bioorganic Chemistry

- Section on Pharmocodynamics—
  John W. Daly, Ph.D.

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system, including: the mechanisms of action of forskolin on adenylate cyclase; development of selective agonists/antagonists for receptors for catecholamines, adenosine, and other neuroregulators; the relationship between membrane potential, phospholipid turnover, and generation of cyclic nucleotides; the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action; and morphologic entities (neurosomes/gliosomes) associated with cyclic nucleotide formation and action. It also conducts research on the effect of drugs on neuronal and muscular function, in particular the transport and function of ions such as sodium, potassium, and calcium, using radioactive alkaloids such as batrachotoxin, histrionicotoxin and pumiliotoxin to investigate sites associated with transport of such ions.

- Section on Oxidation Mechanisms—
  Donald M. Jerina, Ph.D.

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrolase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrument techniques such as high pressure liquid chromatography, high resolution mass spectrometry-gas chromatography, and high-resoluation magnetic resonance in the study of metabolism catalyzed by homogeneous cytochromes P-450, epoxide hydrolase, and the glutathione transferases.

- Section on Neurobiology—
  Phil Skolnick, Ph.D.

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally interact with these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of

endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently under investigation include: (1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined "agonists" and "antagonists;" (2) study of the role of ionophores (*e.g.*, calcium and chloride ions) in neuronal excitability; (3) defining the physiological role of benzodiazepine receptors found outside of the CNS; and (4) the physiologic and pharmacologic modulation of recognition sites and uptake systems in the CNS for psychoactive drugs (*e.g.*, phenethylamines such as amphetamine) and the relationship of such sites to their functional role(s).

National Institute of Child Health and Human Development

Office of the Scientific Director—

- Section on Growth Factors—
  Gordon Guroff, Ph.D.

Investigators in this section are interested in the biochemical and physiological actions of nerve growth factor. This factor has been studied for many years and its function is now clear: it is required for the development and survival of the sympathetic and sensory nervous systems. Without nerve growth factor, these neurons die. The chemistry of nerve growth factor has been completely elucidated, but its mechanism of action, and indeed the mechanisms of action of the more than 30 other growth factors now known, are only dimly perceived.

This group's work involves a dissection of the biochemical events, particularly those in the nucleus, which follow the interaction of nerve growth factor with the cell. The systems used are organ cultures of sympathetic ganglia from neonatal animals and the PC12 cell, a pheochromocytoma clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. In recent years, it has become clear that phosphorylative changes in the proteins of these cells are pivotal events in the actions of the factor. The laboratory is working to isolate and purify the proteins involved and the enzymes carrying out these phosphorylations, as well as to understand the role of these proteins in the structure and transcription of the DNA. The ultimate goal is to define the exact molecular mechanism of these peptide factors. Research is also in progress on the induction of transmitter-synthesizing enzymes, the enzymology of neurite development, and the actions of growth factors on the central nervous system.

Laboratory of Developmental Neurobiology

Phillip G. Nelson, M.D., Ph.D.

Research in neurobiology is conducted using tissue cultures of normal and neoplastic nerve and muscle. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. The membrane mechanisms of action of some neuroactive peptides are under investigation. In addition, molecular genetic techniques are being applied to problems of nervous system development.

- Section on Neuroendocrinology—
  David C. Klein, Ph.D.

Investigations in this section focus on the molecular mechanisms through which neuro-transmitters regulate gene expression, using cultured pinealocytes as the primary experimental model. There are three areas of activity. First, the adrenergic control of pineal cyclic AMP and cyclic GMP is studied; both cyclic nucleotides are regulated by α-adrenergic potentiation of β-adrenergic stimulation. Second, the role of membrane protein phosphorylation in transsynaptic signal transduction is investigated. And third, recombinant DNA techniques are being used to study how enzymes involved in the conversion of tryptophan to melatonin are regulated.

Laboratory of Developmental Pharmacology
Daniel W. Nebert, M.D.

This laboratory investigates gene expression, with special emphasis on enzymes that metabolize drugs, chemical carcinogens, and other environmental pollutants. Molecular genetic and recombinant DNA techniques are used to study differences in the expression of these genes among inbred mouse strains, as well as wild-type and variant cells in culture. Nucleotide and amino acid sequences, evolution, tissue and developmental specificity, the role of enhancer sequences, and DNA-binding regulatory proteins such as inducer-receptor complexes are examined to learn about fundamental mechanisms involving drug metabolism induction, drug toxicity and teratogenesis, and chemical tumorigenesis and mutagenesis. One long-range goal is to develop recombinant DNA assays for predicting human populations at increased risk for certain types of environmentally induced toxicity, birth defects, and cancers.

Laboratory of Theoretical and Physical Biology
David Rodbard, M.D.

This laboratory studies receptors for hormones and neuropeptides *in vitro,* and analyzes pharmacokinetic processes *in vivo* using stable isotopes with liquid chromatography-mass spectrometry. The Section on Theoretical Biology studies drug-receptor interactions, combining experimental and computer-modeling approaches, including computer-assisted optimization of experimental design. The multiple types and subtypes of the opiopeptide receptor system is the present focus of attention.

The Section on Metabolic Analysis studies the metabolism of calcium, other metals, carbohydrates, steroids, and amino acids in humans to evaluate metabolic correlates of growth and development (*e.g.* effects of growth hormone, sex steroids, and pregnancy).

The Section on Macromolecular analysis develops new methods for fractionation of proteins and polypeptides, using electrophoretic and other physical-chemical methods.

Laboratory of Neurochemistry and Neuroimmunology
Harold Gainer, Ph.D.

This laboratory investigates the biosynthesis, secretion, and mechanisms of action of various biologically active neuropeptides, such as ACTH, α-MSH, β-endorphin, dynorphin, vasopressin, and oxytocin. Techniques employed include immunochemistry, immunoassay, immunocytochemistry, recombinant DNA methodology, protein and peptide separation and chemistry, and microchemistry of small brain areas. The laboratory uses the approaches of cell biology to study the intracellular and extracellular mechanisms which determine the expression of specific neuronal identity (i.e., its endogenous peptides, its particular projection pathways, and its specific termination sites in the central nervous system). Also studied is the development of peptidergic neurons and their relation to the immune system.

Cell Biology and Metabolism Branch
Richard D. Klausner, M.D.

This laboratory focuses on various areas of receptor and membrane biology. One program is aimed at understanding the molecular nature of the transcriptional control elements that determine the expression of the highly regulated human transferrin receptor. Basic techniques of recombinant DNA technology have been employed to clone the gene for this receptor and to analyze the sequences involved in the sensitivity of this gene to pharmacological agents that alter iron availability as well as to growth factors and the state of proliferation of the cell. This highly regulated receptor serves as a model for the molecular aspects of receptor regulation. Two groups are examining the role of specific receptors in the activation and proliferation of T cells. One is studying the structure and function of the murine T cell antigen receptor. This includes the identification, characterization, and purification of each of the six different chains of the receptor complex. Purification is permitting the sequencing of these proteins,

which will allow the molecular cloning of the genes encoding the components of the receptor complex. The structure of the complex in different classes of T cells, during T cell development, and in abnormal T cells is being explored. The receptor undergoes a complex pattern of phosphorylation events upon ligand binding. The nature and function of these events are being dissected by structural and pharmacological approaches, and correlations between receptor phosphorylation, phospholipid turnover, calcium fluxes, and membrane potential are active areas of investigation. The interleukin-2 receptor drives T lymphocyte proliferation in response to the lymphokine IL-2. The gene encoding this receptor has been cloned and the promoter and regulatory regions are being characterized. Particular attention is being focused on understanding the expression of this gene in normal and leukemic T cells. The approaches in the laboratory include lipid and protein biochemistry, immunology, hybridoma technology, recombinant DNA technology, and cell biology.

Endocrinology and Reproduction Research Branch

Kevin J. Catt, M.D., Ph.D.

This branch conducts research into basic aspects of hormone action, with emphasis on the characterization and regulation of cell-surface receptors for peptide hormones and their associated membrane effector systems. Of particular interest are the receptor-mediated mechanisms involved in the regulation of pituitary, gonadal, and adrenal function. Current research includes studies on the receptors and mechanisms of action of hypothalamic and pituitary hormones, and on the control of steroid production in endocrine target cells of the gonads and adrenals. The role of hormones in cellular regulation is also examined in relation to normal and disordered human endocrine function, using *in vitro* systems for the analysis of hormone action and the stimulatory and inhibitory control of target-cell function. Specific areas of study include the role of neuropeptides in hypothalamic-pituitary regulation; the analysis of brain receptors for peptide hormones (angiotension II, GnRH, and CRF); the isolation of receptors for angiotensin, GnRH, and gonadotropins; the hormonal control of granulosa-cell differentiation and Leydig cell function; the renin-angiotensin system and aldosterone secretion; and the phosphorylation mechanisms involved in hormonal and metabolic regulation.

National Institute of Dental Research

Laboratory of Microbiology and Immunology

- Cellular Immunology Section—Sharon M. Wahl, Ph.D.

This section investigates basic mechanisms by which host defenses to microbial and other antigens mobilize and modulate cellular and antibody-mediated inflammatory reactions. A major effort involves the study of hormone-like immunoregulatory factors produced by inflammatory cells. The biological effects and biochemical and molecular characteristics of these inflammatory hormones which are produced by lymphocytes and monocytes and are active at 10^{-10} to 10^{-15} M are being explored. The section is using mediators such as interferon, interleukin 1 and 2, fibroblast activating factor, oxygen metabolism-inducing factors, colony stimulating factor, prostaglandins, thromboxanes, and leukotrienes to modulate inflammatory cell responses *in vitro* and to define mechanisms of immune regulation of connective tissue metabolism. Through the use of pharmacological agents and monoclonal antibodies, it is dissecting the mechanisms by which these mediators activate target cells and initiate the cascade of reactions which amplify the inflammatory process.

Studies of the immunological events associated with AIDS, rheumatoid arthritis, streptococcal cell wall-induced polyarthritis in a rat model, and periodontitis analyze the mechanisms of chronic inflammatory disease and how the course of the disease can be altered by manipu-

lation of the immune system (using steroids, nonsteroidal anti-inflammatory drugs, cyclosporin, etc). Additionally, the use of the mononuclear cell-derived hormone-like mediators (IL2, interferon) in the treatment of diseases such as cancer and AIDS is currently being evaluated clinically and immunologically.

Laboratory of Developmental Biology and Anomalies
George R. Martin, Ph.D.

This laboratory studies the synthesis and degradation of connective tissue and disorders and drugs that alter its normal structure and function. Mouse models of human diseases (such as diabetes, cancer cell metastasis, oral-facial malformation, and brittle bone) are studied and also used as test systems to monitor potential therapeutic approaches. Differentiating cultured cells are used to detect and investigate the teratogenic action of drugs. Particular attention is directed toward genetic and environmental factors which alter the expression of connective tissue genes using recombinant DNA technology.

Neurobiology and Anesthesiology Branch
Ronald Dubner D.D.S., Ph.D.

This branch conducts studies on the neurobiological basis of somatic sensation, with emphasis on pain mechanisms. Neuropharmacological studies examine changes in neurochemical activity at various levels of the nervous system following the production of experimental inflammation in animals. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns, utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Electrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavioral studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of opiates, monoamines, and other putative neurotransmitters in the brain on neural function and animal behavior are studied utilizing this behavior model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacological agents utilized in the control of acute and chronic pain. Present studies include the role of endogenous opioid compounds in stress and analgesia, the mechanism of action and efficacy of tricyclic antidepressant drugs in the control of painful neuropathies, the efficacy of different opiate receptor agonists in the treatment of cancer pain, and the analgesic potency of nonsteroidal anti-inflammatory drugs.

National Institute of Environmental Health Sciences

This institute is the only one of the 11 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Behavioral and Neurological Toxicology
Clifford L. Mitchell, Ph.D.

The research programs of the laboratory are aimed at understanding neuronal plasticity and nervous system mechanisms responsible for adaptation to the environment. This is of particular relevance to toxicology since interference with adaptive mechanisms gives rise to the signs and symptoms produced by a toxicant. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the behavioral, neurochemical, and electrophysiological induces of neural plasticity and adaptation during the development of the nervous system, and their alteration by exposure to environmental agents. Among the substances being

studied are heavy metals, organochlorine pesticides, microwaves, and their interactions with psychoactive drugs.

Laboratory of Molecular Biophysics
Colin F. Chignell, Ph.D.

Research programs of the laboratory cover several areas, including the use of physicochemical techniques to monitor the interaction of chemical agents with biological systems; physical organic and bioorganic chemical studies of environmental agents, biological materials, and their conversion products; and the development and application of mass spectrometry to the identification and quantitation of chemical agents and their metabolities in biological systems. The molecular biophysics program mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current projects include the generation of free-radical intermediates during the metabolism of xenobiotics and the mechanisms of chemically induced photosensitization (phototoxicity and photoallergy). In addition, NMR spectroscopy is being used to study the effects of environmental agents on metabolism and the biotransformation of chemical compounds *in vivo*. An important component of this program is an NMR imaging system which makes it possible to monitor the response of experimental animals to toxic chemicals. Other programs include the biochemistry of prostaglandins and leukotrienes (including the co-oxidation of carcinogens by prostaglandin synthetase and peroxidases); and the metabolic transformation of phthalate esters. The mass spectrometry laboratory is well equipped. Current research in this area includes the analysis of peptides and oligonucleotides by tandem mass spectrometry, the development of combined liquid chromatography-mass spectrometry for the analysis of environmental chemicals and their metabolites, and the application of tandem mass spectrometry to gas phase ion chemistry.

Laboratory of Pulmonary Function and Toxicology
Paul Nettesheim, M.D.

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: (1) regulation of biosynthesis and secretion of mucus glycoproteins; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the noncellar alveolar lining layer in disease; (4) the biology, life cycle, and function of respiratory tract epithelial cells studied with *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

Laboratory of Reproductive and Developmental Toxicology

- Developmental Endocrinology and Pharmacology Section—
  John A. McLachlan, Ph.D.

Investigators in this section study the biology and chemistry of estrogens and estrogenic xenobiotics. A primary interest is the normal and abnormal influences of estrogens on target cell differentiation; permanently altered programs of cell differentiation include atypical expression of gene products and abnormal growth regulation. Studies routinely use fetal or immature mice, organ cultures of fetal target tissues, and primary cultures of epithelial or mesenchymal target cells. Cell cultures are used to determine the mechanisms of estrogen-induced neoplastic cell transformation. Areas of interest include genital tract pathobiology, hormone-associated growth factors, hormone-induced gene action, regulation of cell proliferation, estrogen receptors,

structure-activity relationships of estrogenic chemicals, and target organ metabolism of estrogens.

Laboratory of Reproductive and Developmental Toxicology

- Experimental Teratogenesis Section—
  Robert M. Pratt, Ph.D.

Studies in this section deal primarily with rodent embryonic and fetal development and the mechanisms by which various environmental agents and drugs interefere with normal development. Emphasis is placed on the development of the craniofacial region and the biochemical and molecular bases for sensitivity to teratogens using cell, organ, and whole-embryo culture in conjunction with biochemical, morphologic, pharmacological, and toxicologic approaches. Of special interest is the manner in which various hormones and growth factors (EGF) influence normal and abnormal development of embryonic and fetal tissues. Also of interest are the biochemical and molecular factors predisposing embryos to the teratogenic effects of agents such as steroids, retinoids, and dioxins (TCDD).

Laboratory of Reproductive and Developmental Toxicology

- Reproductive Neuroendocrinology Section—
  Andres Negro-Vilar, M.D., Ph.D.

Research in this section is directed toward understanding and defining the endocrine paracrine, and autocrine roles of peptides and amines within the hypothalamic-pituitary-gonadal axis. Several levels of integration are considered. At the subcellular level, the mechanisms involved in modulation of peptide hormone release are evaluated by analyzing activation of aminergic receptors, membrane phospholipid breakdown, calcium mobilization, and activation of other intracellular messenger systems, and correlating those events with peptide hormone release. At the cellular level, potentiation or cooperation between peptides and amines to modify hormone release is also studied. *In vivo* studies include an analysis of the neurotransmitters and modulators that regulate or modify the pulsatile secretory pattern of different peptide hormones, definition of the role of opioid peptides in the regulation of pituitary and gonadal function, and investigation of the effects of stress or selected neurotoxins on central monoamine metabolism and in the secretion of pro-opiomelanocortin-derived peptides and other pituitary hormones.

National Institute of Neurological and Communicative Disorders and Stroke

Laboratory of Experimental Neuropathology

Henry deF. Webster, M.D.

The Cellular Neuropathology Section conducts research on cellular and subcellular mechanisms of myelin formation and maintenance. It develops and uses a broad range of techniques to identify abnormalties in myelin structure, chemistry, and functions that lead to myelin breakdown of the type seen in multiple sclerosis, other demyelinating diseases, and experimental myelin lesions. It also investigates cellular mechanisms of myelin regeneration, especially those relevant to the central nervous system.

The Neurotoxicology Section conducts basic research on toxins which induce disease or malfunction of the central and peripheral nervous systems. Among its goals are to elucidate cellular and subcellular mechanisms of neurotoxin actions and to develop correlations between neurotoxicity and dysfunctions in behavior and biochemistry. Researchers in this section investigate toxic mechanisms of neurological disease, conducting collaborative studies with other clinical or basic science components of the National Institute of Neurological and Communicative Disorders and Stroke as appropriate. Finally, this group

utilizes neurotoxins to develop animal models of neurological disorders.

Laboratory of Neurophysiology
Jeffrey L. Barker, M.D., and
Thomas G. Smith, Jr., M.D.

The principal aim of this laboratory is a multidisciplinary analysis of the cellular properties of specific CNS neurons and the pharmacologic effects of clinically important drugs on these properties. Most of the research is conducted using monolayer cultures of neurons dissociated from different regions of the embryonic CNS. The methods employed are primarily electrophysiologic, including intracellular recording, voltage-clamp, and patch-clamp techniques, although other methods, including biochemical and morphologic, are also utilized. Specific projects include the comparison of chemically and electrically excitable membrane properties in CNS neurons and the effects of clinically important drugs on these properties, the identification of specific cell types using immunohistochemical and biochemical methods, and the separation of specific populations of neurons using fluorescence-activated cell sorting techniques.

Developmental and Metabolic Neurology Branch—

- Membrane Biochemistry Section—
  Peter H. Fishman, Ph.D.

This section's research involves the biosynthesis, organization, and function of cell surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. The hormone-stimulated adenylate cyclase system is used as a model for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process which leads to stimulation of adenylate cyclase on the cytoplasmic side of the membrane. Prolonged stimulation results in both desensitization, where the transduction process becomes attenuated, and in down-regulation, where the receptors become internalized and degraded. The section also is exploring the bio-synthesis and function of complex glycosphingolipids known as gangliosides. Gangliosides can function as receptors for bacterial toxins and may be bio-transducers of both positive and negative signals which regulate cell growth and differentiation.

Experimental Therapeutics Branch—

- Pharmacology Section
  Thomas N. Chase, M.D.

Clinical and preclinical studies are directed toward the development of improved therapies for dementing and extrapyramidal diseases. Transmitter pharmacology strategies concentrate on the dopamine system and closely interactive peptidergic pathways. Information from positron emission tomography allows the localization and biochemical characterization of brain transmitters. These findings give rise to pathogenetic hypotheses, linking an abnormality in a specific transmitter system with the presence of a particular neurological sign. Following evaluation in various animal models as well as in patients using selective pharmacologic probes, such hypotheses motivate the design of novel pharmaceutical interventions for preclinical studies and clinical trials. Current preclinical projects include biochemical and behavioral studies of dopamine-cholecystokinin system interactions; synthesis and testing of the selective inhibitors of cholecystokinin-octapeptide degrading enzyme; and examination of the effects of selective D-1 or D-2 dopamine agonists and antagonists on motor behavior and central dopaminergic and nondopaminergic mechanisms. Ongoing clinical projects include mapping of cerebral muscarinic receptors in Alzheimer's disease under basal conditions and in response to cholinergic agonists; evaluating the effects on cognitive and motor function of a drug which depletes brain somatostatin; and pharmacokinetic and pharmacodynamic studies of the on-off response in Parkinsonian patients.

- Biochemical Neuropharmacology Section—
  John W. Kebabian, Ph.D.

The Biochemical Neuropharmacology Section studies the biochemical mechanisms underlying the activity of recep-

tors for neurotransmitters. There is a special interest in dopamine receptors found in brain and simpler peripheral endocrine tissues. The section studies both the D-1 and D-2 dopamine receptors in simple peripheral tissues and the central nervous system.

- Physiological Neuropharmacology Section
  Judith R. Walters, Ph.D.

Studies in the Physiological Neuropharmacology Section are directed toward investigation of the effects of drugs on neuronal activity and neurotransmitter function in the CNS, especially in the basal ganglia and associated areas, including the substantia nigra, striatum, and globus pallidus. Extracellular single-unit recording procedures and iontophoretic techniques are employed to explore the effects of drugs and neurotransmitters on the activity of single neurons *in vivo* in the anesthetized rat, and *in vitro* in brain slices. Currently, the functions of dopamine, GABA, and peptide-containing neurons in these brain regions are being investigated, with special focus on modulatory interactions between different neurotransmitter systems and the consequences of agonist and transmitter-induced stimulation of specific transmitter receptor subtypes. Neurophysiologic determinations are combined with chronic or acute drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

Unit on Neuroendocrinology
Thomas L. O'Donohue, Ph.D.

Investigations in this laboratory focus on the cellular biology and molecular pharmacology of peptidergic neurons. A major focus is defining the signal transduction mechanisms which link cell-surface receptors to the nuclear processes that regulate transcription of neuropeptide and peptide hormone genes. These experiments involve techniques for receptor analysis, protein and phosphoprotein identification, molecular cloning, DNA sequencing, binding and mutagenesis experiments, and gene transplantation studies. A second series of studies is directed at the isolation and characterization of members of a new family of neuropeptides that interact with the phencyclidine and sigma opioid receptors. These studies utilize techniques for peptide isolation and sequencing, immunocytochemistry, autoradiography, and receptor binding.

National Institute on Alcohol Abuse and Alcoholism

Laboratory of Clinical Studies

Markku Linnoila, M.D., Ph.D.

The laboratory consists of a 10-bed research ward, 11 modules of laboratory space, and an animal facility in the NIH Clinical Center. There are five sections and two units in the laboratory. The major research interests consist of treatment and prevention of alcoholism and alcohol withdrawal. New medications with specific mechanisms of action will be tried in detoxication and maintenance treatments of alcoholics. Both the pharmacokinetics and pharmacodynamics of the drugs are carefully monitored 24 hours a day with EEG, ECG, and BP telemetry as well as temperature and activity measurements. Cerebrospinal fluid, plasma and urine monoamines, and prostaglandins are quantified with mass fragmentography and liquid chromatography. Peptide neuromodulators are measured with radioimmunoassays after separation with chromatography. Receptor functions are measured in blood cells and in animal experiments. Brain functioning is measured with electrophysiological and imaging techniques over and beyond behavioral observations. Liver functioning will be characterized using C_{13}-labeled drugs as tools to evaluate metabolic rates of both flow- and enzyme-dependent drugs. Preclinical tests of drugs having potential for treatment of alcoholism will be conducted in the Neuroscience Section of the laboratory. The Unit of Genetic Studies will use two-dimensional protein electrophoresis to detect polymorphisms in

families with alcoholics and subsequently will engage in chromosomal mapping.

Laboratory of Preclinical Studies
Forrest F. Weight, M.D.

Research investigations in this laboratory center on the physiology and pharmacology of neurons and synapses in the central and peripheral nervous systems. The general areas studied include: regulation of nerve cell excitability and neurotransmitter release, cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin, and GABA; membrane mechanisms of neurotransmitter and drug actions; cellular actions of peptides such as enkephalins, endorphins, and LH-RF; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbituates, opiates, and other neuroactive substances. The research techniques available to a medical staff fellow include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations, such as CNS slices, sympathetic ganglia, and tissue culture for studying the pharmacology of drug-receptor interactions; voltage and patch-clamp techniques for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

National Institute of Mental Health

Laboratory of Cerebral Metabolism

- Section on Developmental Neurochemistry—
  Louis Sokoloff, M.D.

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states. Methods for the measurement of other biochemical processes in the brain *in vivo* are under development.

Laboratory of Molecular Biology

- Section on Regulatory Proteins
  Werner A. Klee, Ph.D.

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that normally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase complexes, including especially GTP binding and hydrolyzing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

- Section on Biophysical Chemistry
  David M. Neville, Jr., M.D.

This section studies protein toxins such as ricin, diphtheria, and tetanus toxin. Particular emphasis is given to the receptor-mediated entry processes to the cytosol compartment. These pathological processes are viewed as analogous to physiologic protein and peptide transport thought to be involved in signaling events. In conjunction with the basic program the section designs, synthesizes, and tests monoclonal antibody-toxin conjugates (immunotoxins) for use as therapeutic reagents in eliminating unwanted cell types from mixed-cell populations. Current goals are to increase the therapeutic ratio of immunotoxins to permit *in vivo* use. Design considerations will utilize newly acquired knowledge on toxin entry mechanisms. Active collabo-

rations with clinical groups are maintained.

Laboratory of Neurochemistry
Seymour Kaufman, Ph.D.

The main effort of this laboratory is devoted to studies of the regulation of the synthesis of the biogenic amine neurotransmitters dopamine, norepinephrine, serotonin. Current research involves the molecular characterization of the phenylalanine, tyrosine, and tryptophan hydroxylases—the enzymes that catalyze the rate-limiting steps in the biosynthesis of these neurotransmitters—as well as the enzymes involved in the biosynthesis of the coenzymes that are essential for these reactions, tetrahydrobiopterin. The researchers are studying the regulation of these enzymes by hormones, drugs, membrane depolarization, and diet, using techniques such as HPLC and affinity chromatography and tools such as monoclonal antibodies. Also being investigated is the regulation of the activity of these enzymes with the aid of recombinant DNA technology and genetically engineered proteins.

Biological Psychiatry Branch
Robert M. Post, M.D.

This laboratory is engaged in studies of the clinical and behavioral pharmacology of various psychotropic drugs, particularly antidepressants, antipsychotics, anxiolytics, and anticonvulsants. The anticonvulsant carbamazepine has recently been found to have acute and prophylactic effects in both phases of manic-depressive illness. Studies are aimed at elucidating the possible mechanisms of action of this drug in seizure and affective disorders based on studies of clinical populations and laboratory animals.

Investigators work in a multidisciplinary laboratory environment where active interchange among clinicians and basic scientists is encouraged. The laboratory component (which could form the entire fellowship experience or be integrated with a clinical phase) could also involve studies of the behavioral pharmacology of chronic psychomotor stimulant administration and the neural mechanisms underlying long-term behavioral and physiological changes observed in electrophysiological kindling and in learned helplessness. Techniques of clinical pharmacology, biochemistry, and behavioral analysis, with a particular focus on the roles of conditioning and learning mechanisms in long-term changes in behavior, would be emphasized. The fellows would be able to learn techniques of behavioral pharmacology, animal modeling, biochemistry, and physiology based on *in vivo* and tissue-slice preparations, and would study the biochemistry of classical neurotransmitters and peptides and their receptors using a variety of techniques, including receptor autoradiography. The fellowship would involve intensive individual work on one or more projects that would be designed, conducted, presented, and written up for publication by the fellow under the supervision and tutelage of the preceptor.

Biological Psychiatry Branch—
Agu Pert, Ph.D.

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits that control specific behaviors. Methods used include extracellular single-cell recording as well as iontophoretic techniques with drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Current emphasis is on two projects: the actions of endorphins and enkephalins on brain function, especially the processing of pain information; and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptors sensitivity.

Laboratory of Cell Biology
Michael J. Brownstein, M.D., Ph.D.

The members of this group want to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, they want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products. The investigators hope to show how these processes are regulated by hormones and neurotransmitters at the

transcriptional, translational, and post-translational levels. Finally, they are engaged in characterizing neurotransmitter receptors in order to determine more about the molecular basis of signal transduction.

- Section on Pharmacology—
  Julius Axelrod, Ph.D.

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of hormone and neurotransmitter secretion, methylation reactions, and signal transduction mechanisms.

- Section on Biochemical Pharmacology—
  Martin Zatz, M.D., Ph.D.

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated, and the other concerns the regulation of membrane metabolism by light and neurotransmitters. Related topics include brain inositide and cyclic nucleotide metabolism, Vitamin A and photoreception, and the pineal gland. Biochemical and pharmacologic approaches to these problems are emphasized.

Clinical Neuroscience Branch

- Section on Preclinical Studies
- Section on Molecular Pharmacology
  Steven M. Paul, M.D.

The major research interests of these sections involve characterizing and defining the basic neurochemical and electrophysiological mechanisms of synaptic transmission, as well as the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with these mechanisms. Many studies involve characterization of neurotransmitter and drug receptors and recognition sites, characterization of ion channels, and definition of the relevant interactions of psychotropic drugs with these membrane proteins. Several receptor-effector systems and drug recognition sites are currently under investigation, including receptors for benzodiazepines/GABA, tricyclic antidepressants, psychomotor stimulants (amphetamine, methylphenidate), acetylcholine, serotonin, adenosine, and various neuropeptides (*e.g.* cholecystokinin). The role and regulation of these systems are investigated by (1) biochemical and pharmacological characterization of the recognition sites (including purification of receptor protein using affinity chromatography), defining receptor subunits by gel electrophoresis and radiation inactivation, and the production of selective monoclonal antibodies to define functional receptor domains labeled by various radioligands; (2) isolation and characterization of the endogenous modulators of these sites using multiple chromatographic methods; (3) development of appropriate *in vitro* models for studying these receptor-effector systems (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacological experiments in animals (J. Crawley); (6) genetic studies in inbred strains of rats and mice, couple with an examination of receptor-receptor-effector changes in correlation with the behavioral manifestations of these genetic mutations; (7) post-receptor events, including calcium transport, cyclic nucleotide changes, and agonist-induced phosphatidylinositol hydrolysis, and (8) electrophysiological experiments using single-unit recording techniques (L. Skirboll, D. Hommer) which are integrated with the biochemical studies in an attempt to relate these findings to physiological changes in neuronal excitability.

- Section on Brain Biochemistry—
  Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. This section uses radiolabeled ligands with fully preserved biological activity to study drug

and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain tissue in which neuroanatomical relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus, with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (*e.g.,* angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of laboratory's efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

Laboratory of Clinical Science

- Section on Clinical Pharmacology
  Juan M. Saavedra, M.D.

This section's research program focuses on three areas: the central mechanisms involved in the control of pituitary function and sympathetic activity, the localization and characterization of brain neuropeptide and amine receptors by quantitative autoradiography, and the regulation of the immune system by sympathetic nerves and hormones. The scientists use a combination of microanalytical techniques, radioenzymatic assays, radioimmunoassays, and high pressure liquid chromatography to study the metabolism of biogenic amines and neuropeptides in selected brain areas of several experimental and genetic animal models. The section is also interested in the utilization and development of image analysis techniques with computerized microdensitometry for autoradiographic quantitation and characterization of receptors for neuropeptides and biogenic amines in single nuclei of rat and human brain cells.

- Section on Histopharmacology
  David M. Jacobowitz, Ph.D.

This section studies the basis of behavioral regulation and pathological changes by a multidisciplinary approach to CNS neurotransmitter or neurochemical systems. Histochemical, neurochemical, and physiological analyses are carried out at the level of discrete brain regions and pathways in order to define the underlying basis for behavioral changes, drug effects, and sexual and aging differences. Drugs, stress, electrical stimulation, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, peptides, proteins, and enzymes are measured within specific nuclei, tracts, and other discrete regions of the brain using a microdissection method, radioisotopic assays, and immuno-cytochemical methods. Two-dimensional gel electrophoresis and column chromatography are being used for the isolation and purification of brain proteins.

Laboratory of Preclinical Pharmacology

- Section on Neuropeptides—
  Hsiu-Ying T. Yang, Ph.D.

This section is concerned with research on the neuropeptides in the brain and peripheral nervous system. Current studies are on the characterization of the enzymes involved in the metabolism of enkephalin and related peptides. Based on the characteristics of these enzymes, their inhibitors are searched for and used to aid in exploring the role of endogenous opioid peptides. The role of endogenous opioid peptides in analgesia, the mechanism of morphine tolerance, and the interaction of opiates with other neuropeptides are also being investigated.

- Group on Immunochemistry
  De-Maw Chuang, Ph.D.

This group conducts research in several areas related to molecular neuropharmacology. These include studies on: (1) molecular events of internalization of β-adrenergic receptors in cells desensitized with β-adrenergic agonists; (2) mechanisms of action of antidepressant drugs with emphasis on the physiological and pharmacological roles of high-

affinity recognition sites for these drugs; and (3) regulation by neurotransmitters and neuromodulators of phospholipid metabolism by phospholipases A2 and C in cultured tumor cells, rat aorta, and brain slices. This laboratory also uses hybridoma and cDNA techniques to quantitate neuropeptide mRNA levels.

National Institute of Mental Health

Alcohol, Drug Abuse, and Mental Health Administration

Shervert Frazier, M.D.
Director
Frederick K. Goodwin, M.D.,
Director, Intramural Research
Dennis L. Murphy, M.D.
Associate Director for Clinical Research
Seymour Kety, M.D.
Associate Director for Basic Research
Richard J. Wyatt, M.D.
Associate Director for Research
at Saint Elizabeths Hospital
Rex W. Cowdry, M.D.,
Clinical Director
Llewellyn B. Bigelow, M.D.
Associate Clinical Director for
Research at Saint Elizabeth's Hospital

The National Institute of Mental Health (NIMH) offers an opportunity for post-doctoral research training in psychiatry and in the biologic and behavioral sciences. The NIMH intramural program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Some medical staff fellows conduct clinical and/or basic research, and are responsible for the clinical care of patients admitted for research and therapeutic purposes. Other fellows engage primarily in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All medical fellows participate in tutorial seminars and other teaching programs as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all medical staff fellows to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Appointments in Clinical Research

The NIMH recruits about 12 new medical staff fellows each year who are primarily involved in clinical research. Appointments normally begin July 1 and are usually for 2- or 3-year periods, although in some instances they may be extended.

Fellows usually begin their appointments after the PGY-3 or PGY-4 level of residency training. Exceptionally well-qualified individuals, however, may be appointed after PGY-2 level of residency training in psychiatry, neurology, or other clinical specialties. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Medical Staff Fellowship Program are now being accepted for July 1988 appointments. Since selections for these positions will be made in January 1987, PGY-2 or PGY-3 psychiatric residents may now apply.

Medical staff fellows usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly

clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the fellow and the status of the clinical research program. Intensive clinical supervision on the inpatient psychiatric unit is available from senior psychiatrists. Candidates desiring more information about clinical fellow positions should write to Rex W. Cowdry, M.D., NIMH, Building 10, Room 3N234, National Institutes of Health, Bethesda, MD 20892.

Appointments in Laboratory Research

Some fellows work primarily in the laboratory under the preceptorship of a senior staff scientist. They are usually assigned to a basic science laboratory for intense training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about these positions in the neurobiologic area, contact the chief of the particular basic science laboratory or section at the National Institutes of Health, Bethesda, Maryland 20892. For information in the psychosocial area, contact Marian Yarrow, Ph.D., NIMH, Building 15K, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Clinical and Basic Research Branches

Biological Psychiatry Branch—
Robert Post, M.D.

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including manic-depressive and schizo-affective illness, panic-anxiety disorders, menstrually related mood disorders, and suicidality. The focus of the branch is psychobiologic and brings together information from the following disciplines—psychiatry, psychology, neurology, genetics, pharmacology, and biochemistry. Longitudinal evaluation of the course of illness and response to treatment is an important clinical and research methodological approach. Some specific research interests are psychogenetics, the biochemistry of neurotransmission, neuroendocrinology, investigations of perception and cognition, cerebral tomography of average evoked potentials, and positron tomography. A general goal of this branch is to develop programs to investigate psychologic, biochemical, and neuroanatomic contributions to the study of manic-depressive illness, anxiety disorders, and related symptoms.

Fellows will be trained in clinical research methodology, data analysis, and clinical management of research patients.

Opportunities are also available for studying behavioral and biochemical laboratory techniques with Drs. Agu Pert and Paul Marangos.

- Section on Psychobiology
  Robert M. Post, M.D.

This 14-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients

with manic-depressive and schizoaffective illness and rapidly cycling phenomena. Medical staff fellows are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduct, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies, such as the measurement of amine metabolites, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely coordinated with several biochemical laboratories. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including noradrenergic receptor agonists, anticonvulsants such as carbamazepine, and several endogenous polypeptides. The mechanisms underlying the paradoxic antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis. Dr. Agu Pert also conducts major programs on behavioral pharmacology, *in vivo* receptor autoradiography, and the interaction of peptide and neurotransmitter mechanisms.

- Section on Neuroendocrinology
  Philip W. Gold, M.D.

The work of the section on Neuroendocrinology is conducted in three settings. First, on the clinical research unit of the Biological Psychiatry Branch, neuroendocrine studies in patients with affective illness and normal controls focus on corticotropin releasing factor and its interactions with other peptides, particularly the endogenous opiates and the neurohypophyseal hormones, arginine vasopressin and oxytocin. A second setting is the clinical research unit of the Developmental Endocrinology Branch of the NICHD, which studies clinical neuroendocrine disorders such as Cushing's disease, Addison's disease, and various conditions characterized by hypothalamic-pituitary gonadal dysregulation. Members of the section make rounds on this ward and participate in active collaborative research. A particular focus is the study of the pathophysiological analogies between Cushing's disease and depression. The third setting is the Preclinical Laboratory, which has an active program to measure a variety of neuropeptide hormones, including CRF, ACTH, β-endorphin, arginine vasopressin, and oxytocin, and which conducts studies of neuroendocrine regulation in laboratory animals and subhuman primates. Each associate will spend considerable time in each of these settings in order to have a well-rounded experience in the scope and techniques of psychoneuroendocrinology.

- Unit on Anxiety and Affective Disorders—Thomas W. Uhde, M.D.

This unit is engaged in the clinical and laboratory study of patients with anxiety and affective disorders. Most clinical research is conducted in the new Ambulatory Care Research Facility (ACRF), although intensive diagnostic assessment and drug treatment is available to patients on the 14-bed inpatient unit of the Biological Psychiatry Branch. A major emphasis is on the phenomenology, life course, familial patterns, and psychobiology of panic disorder, including agoraphobia with panic attacks. Particular attention is given to the study of possible "state" or "trait" markers of pathological anxiety and the testing of new anxiolytic agents. Current biologic correlates of interest include galvanic skin response, evoked potentials, sleep architecture, pain sensitivity, ^{3}H-imipramine and ^{3}H-dihydroergocryptine binding to the platelet and the neuroendocrine responses to agents with relatively selective effects on noradrenergic and other neurotransmitter systems. Drugs currently

under study include alprazolam, caffeine, carbamazepine, clonidine, diazepam, propranolol, RO 15-1788, and yohimbine.

- Unit on Peptide Studies—
  David R. Rubinow, M.D.

This unit is involved in investigating basic mechanisms and clinical manifestations of endocrine and peptide effects on mood, cognition, and behavior. The interface between medicine and psychiatry is explored in a variety of inter-Institute collaborative research projects established through the NIMH consultation-liaison service. An additional major focus is the biological characterization and treatment of menstrually-related mood disorders.

Clinical Psychobiology Branch—
Thomas A. Wehr, M.D.

Clinical research is conducted in areas related to affective illness (depression and mania) and sleep disorders. Laboratory research involves studies of the neurobiology of sleep and circadian rhythms. Structurally the branch is divided into the Clinical Research Unit, the Unit on Sleep Studies, and the Outpatient and Follow-up Unit. Throughout the 2- to 3-year assignment, the fellow's time is divided among clinical care-ward management, clinical research, and laboratory research, depending on interest. Direct responsibility for research projects is assumed from the beginning.

- Clinical Research Unit—
  Thomas Wehr, M.D.

The unit represents the major research resource of the branch and is located in a 15-bed psychiatric research ward.

The major focus of clinical research on the inpatient unit is the treatment of affective disorders and the investigation of abnormalities in the timing and phase of circadian rhythms in depression, mania, and sleep disorders.

Both pharmacological and nonpharmacological treatment strategies are studied. For example, the effects of antidepressants and thyroid hormone on the cycles of mania and depression are currently being evaluated. Non-pharmacological treatments include sleep deprivation, altering sleep schedules, and manipulation of environmental light. We have the capability of studying similar interventions in normal volunteers and animals. We are evaluating the possible synergistic effects of medications and non-pharmacologic treatments. Neuroendocrine studies involving, for example, the thyroid and adrenal and the effects of light on melatonin secretion are being conducted.

The characteristics of circadian systems in patients and normal volunteers are studied in conditions where they are isolated from all time cues for periods up to 4 weeks. New techniques and instruments make it possible to study continuously changes occurring in motor activity, body temperature and EEG-recorded sleep.

- Outpatients and Follow-up Unit—
  Norman Rosenthal, M.D.

A common theme of both inpatient and outpatient studies is the longitudinal study and treatment of cyclical affective disorders and sleep disorders. Outpatients with affective disorders are followed in the clinic and admitted for psychobiological and treatment studies. We encourage the study and treatment of interesting subgroups. For example, patients who regularly become depressed during certain seasons have been identified and are studied and treated biologically and psychologically.

- Unit on Sleep Studies—
  Wallace Mendelson, M.D.

This unit conducts studies of sleep physiology and pharmacology, with emphasis on the role of sleep in psychiatric illnesses such as depression. Other areas of concern are sleep as a circadian rhythm and primary pathologies of sleep such as sleep apnea syndrome. Psychophysiologic studies of insomnia and hypersomnia are pursued at a clinical level. Animal sleep studies involve experimentation with possible naturally occurring "sleep factors" and the role of benzodiazepine receptors in sleep and anxiety. Electronic analysis of the EEG is done at both clinical and animal levels.

Clinical Neuroscience Branch—
Steven M. Paul, M.D.

The branch conducts a multidisci-

plinary program in basic and clinical neuroscience and attempts to integrate data on the biochemistry and pharmacology of the central nervous system with an understanding of the pathogenesis and treatment of major psychiatric diseases. Structurally the Neuroscience Branch consists of four sections: Molecular Pharmacology, Preclinical Studies, Brain Biochemistry, and Clinical Studies. Medical staff fellows are assigned to the clinical research unit, usually for a period of 2 to 3 years. During this time their activities are divided between direct patient care, clinical research, and laboratory research, depending on the interests and talents of the individual. Medical staff fellows will be encouraged to become actively involved in ongoing research projects, as well as to develop their own research protocols as early as possible. Collaborations between individual medical staff fellows and the three basic science sections, on both laboratory and clinical research projects, will also be encouraged. The overall goal of the branch is to create a climate in which sound scientific findings can be applied to an understanding of both normal and abnormal behavior.

- Section on Preclinical Studies—Steven M. Paul, M.D.

The major interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible, basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: (1) biochemical and pharmacologic characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes that correlate with the behavioral manifestations of these genetic mutations; and (7) post-receptor events, including alterations in calcium transport and cyclic nucleotide levels.

- Section on Brain Biochemistry—Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. We use radiolabeled ligands with fully preserved biologic activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain where neuroanatomic relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g. angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of our laboratory efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

- Section on Molecular Pharmacology—Steven M. Paul, M.D., Acting

Current investigations are directed toward an understanding of the regulation and actions of receptors at the cellular level. Two examples of current work are studies of: interactions between GABA receptors and benzodiazepine

receptors; the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity and benzodiazepine receptor purification; and mechanisms that control the number and functioning of b-adrenergic receptors in cultured cell lines and alterations in b-adrenergic receptors that occur following exposure of cells to b-adrenergic agonists (desensitization).

- Section on Clinical Studies—
  David Pickar, M.D.

This unit encompasses the entire inpatient evaluation and treatment of patients on the clinical research unit. Current research problems include investigations of the clinical phenomenology of schizophrenia and the similarities and differences between schizophrenia and schizoaffective disorders. Studies on the role of central and peripheral opioid systems (i.e., enkephalin, b-endorphin) in stress, schizophrenia, and depression, and inpatients with acute and chronic pain are also ongoing. Laboratory investigations on possible peripheral biologic markers in schizophrenia, as well as various affective disorders (i.e., platelet [^{3}H] imipramine binding, serotonin transport, RBC membrane fluidity), are being carried out in hopes of unraveling vulnerability factors in these disorders.

Other areas of interest involve attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of GABA, neuropeptides (such as endorphins and vasopressin), and other neurotransmitter systems for their potential involvement in psychosis; evaluation of new antipsychotic drugs; assessment of pharmacologic and endocrinologic aspects of schizophrenia and schizo-affective illness; immunologic aspects of schizophrenia; study of CAT scan abnormalities; cognitive and psychophysiologic evaluations; and PET scan studies.

Laboratory of Clinical Science—
Dennis L. Murphy, M.D.

This laboratory conducts research on the biochemistry, physiology, and pharmacology of the nervous system and relates these findings to clinical areas in psychiatry, medicine, and neurology. Applicants for the medical staff fellow program in laboratory research should have at least 1 year of clinical training, whereas those interested in clinical research are required to have at least 2 years of postdoctoral training in neurology or psychiatry before arrival for duty.

The research program objectives are attained through the cooperative efforts as well as the independent research of investigators in the various sections and units of the laboratory.

Clinical Neuropharmacology Branch—
Dennis L. Murphy, M.D.

This branch conducts clinical and laboratory studies designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with affective disorders, dementias, obsessive-compulsive symptoms, Alzheimer's disease, and other behavioral disorders. The clinical studies are primarily based on a 10-bed psychiatric research ward. The inpatient investigations are complemented by an outpatient program for the longer-term study of obsessive-compulsive and dementia patients.

Support for the clinical studies includes a biochemistry/neuroendocrinology laboratory and a behavioral assessment and data processing program. Other neurochemical laboratory studies are oriented toward monoamine neurotransmitter metabolism and function and brain peptide interactions with monoamine systems. Facilities for nonhuman primate studies and behavioral studies of drug effects in small animals are also available in the branch.

The ward research investigations, which are balanced between biologic-pharmacologic and psychologic-phenomenologic approaches, take place in the setting of an active clinical treatment program. The incoming medical staff fellow, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the fellow will work with a senior staff member in the planning, design, and

implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research and laboratory approaches to clinical problems. Specific research projects range from psychobiological studies of the characteristics of individuals who do or do not respond to specific drugs and to laboratory or animal studies of the effects of drugs on neurotransmitter receptor functions and other cellular events, including enzyme activity and membrane transport. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include selective monoamine oxidase inhibitors, some natural precursors of brain neurotransmitters, and lithium carbonate, as well as other antidepressants and some new investigational compounds. Special areas of study at present include investigations of adaptational responses to long-term drug administration in neurotransmitter receptors and secondary effector systems; animal models of affective and cognitive disorders; neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; studies of monoamine oxidase; and methods for the assessment of behavioral and psychological states.

- Section on Histopharmacology—David M. Jacobowitz, Ph.D.

A major aim of this section is to study the basis of behavior regulation and pathological changes by a multidisciplinary approach to CNS neurotransmitter or neurochemical systems. Histochemical, neurochemical, and physiological analyses are carried out at the level of discrete brain regions and pathways in order to define the underlying bases for behavioral changes, drug effects, sexual and aging differences. Drugs, stress, electrical stimulation, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, peptides, proteins, and enzymes are measured within specific nuclei, tracts, and other discrete regions of the brain using a microdissection method, radioisotopic assays, and two-dimensional gel electrophoresis. Immunocytochemical methods are used to study the localization of peptides and enzymes in the brain.

- Section on Analytical Biochemistry-Sanford P. Markey, Ph.D.

Projects include (1) the study of a neurotoxin which produces a Parkinsonian syndrome in man (MPTP)—its metabolism, pharmacology in various animal species, and molecular basis of action; (2) the synthesis and pharmacokinetic analysis of stable isotope-labeled neurotransmitters in man; (3) the development of new mass spectrometric techniques suitable for analytical biochemistry, including Fourier transform mass spectrometry; (4) studies on the major urinary metabolite of melatonin, and its assay for developmental studies in neonates, infants, and patients with neurological and psychiatric disabilities, or who receive drugs influencing the sympathetic nervous system.

- Section on Clinical Pharmacology—William Z. Potter, M.D.

The central focus is the study of the mechanisms of action of antidepressants and other psychoactive drugs using integrated biochemical and pharmacokinetic studies in man and animals. At present, clinical studies involve both patients with affective illness and normal volunteers. New biochemically specific drugs are examined to identify common biochemical effects using measures in cerebrospinal fluid, plasma, and urine. Parallel investigations are done in animals in which more invasive and detailed studies of CNS biochemical alterations are possible. Since the noradrenergic and serotonergic systems can be directly or indirectly implicated in the action of all known antidepressants, the pretreatment noradrenergic and serotonergic "tone" of patients with affective illness is contrasted to that in volunteers and those with other psychiatric illnesses. Techniques include assay of antidepressants,

hormones, neurotransmitters, and their metabolites in tissues and body fluids by radioimmunoassay, HPLC, or GC-MS; pharmacokinetic modeling of data in neurotransmitter systems; *in vitro* binding techniques for studying neurotransmitter receptor alterations; and the development of appropriate animal models.

As a complement to studies on the mechanisms of actions of antidepressants, a basic component pursues CNS control of cardiovascular function. Many links between drugs affecting mood disorders and those affecting the cardiovascular system are now established. Under Dr. Saavedra specific CNS catecholamine and peptidergic areas involved in blood pressure regulation are investigated using the latest radio-histochemical methods of visualization and quantitation in animal brain.

- Section on Biomedical Psychiatry—
  David C. Jimerson, M.D.

The section conducts neurochemical, neuroendocrine, and pharmacokinetic experiments and drug trials in neuropsychiatric and psychosomatic syndromes. Current clinical studies focus on anorexia nervosa and bulimia, with both inpatient and outpatient protocols. Laboratory studies involve neurotransmitter and neuroendocrine measurements on blood and cerebrospinal fluid samples from clinical and animal investigations.

Child Psychiatry Branch—
Judith L. Rapoport, M.D.

This Branch studies biological correlates of childhood behavioral and developmental disorders. There is a six bed day and/or overnight hospitalization inpatient program and other beds as needed on a pediatric ward, as well as an active outpatient program.

The focus of the program is on diagnostic biological measurements appropriate for childhood disorders and on the identification of biological risk factors for impulse and developmental disorders.

The program includes studies of the diagnostic assessment and drug treatment of hyperactive/conduct disordered children, pharmacokinetic studies, and studies of neurotransmitter systems via body fluids.

A unit is conducting brain imaging studies, in children with developmental disabilities utilizing a variety of techniques. Another group is studying the diagnosis, treatment response and followup status of children and adolescents with severe primary obsessive compulsive disorder.

Clinical Neurogenetics Branch—
Elliot S. Gershon, M.D.

The clinical neurogenetics branch conducts clinical and basic biologic and pharmacologic studies related to the genetics of manic-depressive illness and schizophrenia. Fellowship positions do not open every year, but are considered in terms of the suitability of the applicant to the area in which he or she wishes to work.

- Section on Clinical Genetics—
  Elliot S. Gershon, M.D.

Clinical investigations include biologic, pharmacologic and psychosocial studies, of patients and their relatives, and/or normal controls. Young people at increased risk of illness, and patients currently in remission, are also studied in attempts to define trait markers of vulnerability. Clinical and related basic laboratory studies are pursued in molecular genetics and in neuroscience. Population genetics and pharmacogenetic investigations are also performed. Current projects include genetic studies of DNA polymorphisms, neuron-like characteristics of cultured lymphoblasts and fibroblasts, neuroendocrine and other responses to pharmacologic challenge, and neuropeptides and neurotransmitters in CSF and blood.

- Section on Biochemical Genetics—
  Carl Merril, M.D.

This section concentrates on studies of genomic and gene product variations and their possible relation to the etiology of inherited disorders. This section introduced the use of silver staining for the visualization of protein gene products separated from complex mixtures by gel electrophoresis increasing the sensitivity of detection of proteins 100 fold. Quantitative computerized microdensitometry has been developed for analyzing two dimensional electrophoretic protein pat-

terns. These analytic techniques have been utilized to demonstrate: multiple quantitative protein alterations in the fibroblasts of patients with the Lesch-Nyhan syndrome; disease-specific proteins in the CSF of patients with Creutzfeldt-Jakob disease, herpes encephalitis, schizophrenia, multiple sclerosis, and Parkinson's disease. Twenty-seven independent polymorphic proteins have also been identified in serum, erythrocytes and fibroblasts. These polymorphic proteins are currently being observed in family studies for linkage to classical genetic markers and inherited diseases. Efforts are underway to further develop the sensitivity and specificity of protein detection methods. Investigations also include small polypeptides of neurobiological interest, such as the neuropeptides and their precursors.

Several diseases with non-mendelian maternal inheritance patterns have been found which may be associated with an abnormal mitochondrial genome. DNA sequencing, endonuclease restriction analysis and analysis of mitochondrial gene products have been initiated to clarify the molecular basis of these maternally inherited disorders.

Laboratory of Cell Biology—
Michael J. Brownstein, M.D., Ph.D.

The members of this group have a variety of research interests. These include light and electron microscope-level neuroanatomy, chronobiology, developmental neurobiology, biosynthesis of biologically active molecules, isolation of novel peptide hormones, and regulation of intracellular processes by chemical messengers.

Laboratory of Developmental Psychology—
Marian Radke-Yarrow, Ph.D.

This laboratory conducts basic and clinical research on the affective, social and cognitive development of children, and on the influences of stressful conditions—biomedical or psychosocial—on the course of development and on children's behavioral organization. Among the risk groups being studied are children of parents with affective disorders. Specific studies focus on normal and deviant emotional development in these children compared with children from healthy families, on the affectively ill parent's functioning in relation to his/her child, and on the development of diagnostic procedures for children 2-5 years of age. In studies of young adolescents, the interaction of physical and endocrine changes and the adolescent's psychosocial functioning is being examined longitudinally.

Laboratory and field studies are conducted. There is an emphasis on the development of methods for the measurement of (a) emotion variables in children, and (b) environmental variables that may influence the course of social and emotional development of children. Much of the research by developmental psychologists and child psychiatrists on the staff is collaborative within the laboratory, with colleagues in other laboratories at NIMH and NIH, and with scientists at universities throughout the country.

Laboratory of Psychology and Psychopathology—
Allan F. Mirsky, Ph.D.

This Laboratory conducts a broad program of basic and clinical research on normal and impaired attention, learning, and memory in both humans and monkeys and on the neurophysiologic and psychophysiologic mechanisms involved in these processes. There is a strong emphasis, as well, on genetic studies in schizophrenia under the direction of Seymour S. Kety, M.D. Studies of attention and autonomic nervous system functioning in schizophrenics and in other patients, and of drug effects on these processes are being done by Theodore P. Zahn, Ph.D.

Investigations of attention and cortical and brainstem event-related potentials in psychiatric and neurologic patients are under way in the laboratory of Connie Duncan, Ph.D. These assays are used to evaluate information processing deficits in these patients. EEG brain imaging studies, in collaboration with many other intramural groups, are actively pursued by Richard Coppola, Sc.D.

Studies on the neurophysiology of attention in monkeys with recording from various parts of the brain and with stimulation and ablation techniques are focused on the investigation of animal models of cognitive processes that may be impaired in many human neuropsychiatric disorders. These are directed by Richard Nakamura, Ph.D. Parallel studies of cognitive processes in psychiatric and neurologic patients and in normal controls using similar behavioral techniques are designed to permit direct comparison with the animal work.

Laboratory of General and Comparative Biochemistry—
Giulio L. Cantoni, M.D.

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section on Alkaloid Biosynthesis—
  S. Harvey Mudd, M.D.

This section studies the enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism—
Louis Sokoloff, M.D.

- Section on Developmental Neurochemistry—
  Louis Sokoloff, M.D.

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic, pharmacologic, and pathologic states.

Laboratory of Neurochemistry—
Seymour Kaufman, Ph.D.

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy, including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology—
Steven P. Wise, Ph.D., Acting

This laboratory combines the techniques of electrophysiology, neuroanatomy, neurotransmitter receptor localization, and experimental psychology in studies aimed at understanding the brain circuits, cell types, and receptor mechanisms relevant to neuropsychiatric illness. Research is organized in four units.

- Unit on Motor Systems—
  Stephen P. Wise, Ph.D., Acting

This unit is engaged in studies of single nerve cell activity in basal ganglia, cerebellum, thalamus, and mortor cortex of monkeys performing learned movements. The aim of the work is to achieve an

understanding of the way in which the activity of these structures is integrated during normal movement and how diseases within these structures impair movement.

- Unit on Dynamic Brain Structure—
  Miles Herkenham, Ph.D.

Traditional neuroanatomical techniques reveal features of static morphology; however, the use of fresh brain cut into sections in the cryostat enables studies of the localization of neurotransmitter and drug receptors, enzymes, 2-deoxyglucose metabolism, and architecture. This unit is engaged in studies of correlative, comparative, and developmental features of opiate receptor localization revealed by autoradiography. Related neurochemical and metabolic markers are visualized to show the interaction of the opiate system with other brain systems during normal development and function, after experimental manipulation or in cases of disease-induced abnormalities.

- Unit on Cerebral Cortex—
  Steven P. Wise, Ph.D.

Work in this unit combines techniques of basic neurobiology with techniques of single cell recording in operantly conditioned rats and monkeys. The aim of the work is to discover how the different topographic divisions of the sensorimotor cortex interact in behaving organisms. Special attention is devoted to the different sorts of sensory information that are processed in different subdivisions of the sensorimotor cortex and to how behavioral set and intention for future action are reflected in regions such as the premotor and supplementary motor areas of the cerebral cortex. Specialized neurobiologic techniques (e.g., intracellular injection of neuronal markers and laminar electrophysiologic analysis) are carried out in parallel with the behavioral studies.

Neuropsychiatry Branch—
Richard J. Wyatt, M.D.

This clinical research branch, located primarily at the William A. White Building, St. Elizabeths Hospital, capitalizes on many disciplines in its effort to understand and treat schizophrenia, the psychiatric problems of the elderly, central nervous system regeneration, memory, sleep, and its disorders. The laboratory is set up so that small groups of young scientists may employ biochemical, structural, anatomic, pharmacologic, physiologic, and psychologic techniques in their work with these basic science and clinical problems.

The major focus of the branch's research takes place on three inpatient research wards. Llewellen B. Bigelow, M.D., is the clinical director. There is substantial opportunity to examine drug-free patients and to use pharmacologic probes to discern different patient groups. Three 12-bed research wards housed in the William A. White Building are devoted to schizophrenia and neuropsychiatric research. There is also an outpatient department. In addition, many of the 1,800 inpatients at Saint Elizabeths Hospital participate in research programs.

- Clinical Psychopharmacology Section—
  Richard J. Wyatt, M.D.
  Farouk Karoum, Ph.D.

This section uses quadruple mass spectrometers to measure monoamines and their metabolites in brain plasma, cerebrospinal fluid, and urine of psychiatric patients. High-pressure liquid chromatography is used for the measurement of haloperidol and its metabolites in brain and plasma of schizophrenic patients. Radioreceptor assays are employed for measuring binding sites and receptors in the post-mortem brains of psychiatric patients.

- Section on Aging
  Richard J. Wyatt, M.D.
  Dilip Jeste, M.D.

This section has concentrated on Alzheimer's Disease and tardive dyskinesia in living subjects. Post-mortem studies are in progress in brains of patients with Huntington's Chorea and elderly normal controls.

- Section on Preclinical Neurosciences—
  William J. Freed, M.D.,

This group emphasizes the exploitation of brain grafting techniques to correct lesion-induced behavioral deficits. Currently under study are the characteristics

of the brain as a site of transplantation and the potential of brain grafts to effect functional reconstitution. A major success has been in grafting adrenal medulla or substantia nigra to the caudate nucleus, thereby correcting the rotational behavior that develops following unilateral substantia nigra lesions. Destruction of the substantia nigra has been considered by many to be an animal model of Parkinson's disease, and this group is applying these techniques to rats and monkeys in order to develop brain grafting within this model. Other related interests involve the transplantation of endocrine tissue and retinae to the rat brain.

Although fiber sprouting is always observed following peripheral nerve injury, the functional consequences of such injury are variable, and in mammals, functional recovery is frequently slow and incomplete. This group is interested in developing new approaches to peripheral nerve repair, in order to improve the rate and degree of functional recuperation, and to better understand the mechanisms involved in promotion and obstruction of peripheral nerve regeneration in mammals.

- Clinical Neuropsychiatry Section—
  Daniel R. Weinberger, M.D., and
  Janice R. Stevens, M.D.

This group is investigating the relationship of behavior and psychopathology to neuroanatomic and neurochemical alterations in the brains of patients with neuropsychiatric disorders, principally schizophrenia. In living subjects, the emphasis in on linking brain structure, metabolism, and function to develop more meaningful dimensions of psychiatric syndromes. Powerful new techniques that are currently utilized include computed tomography, xenon-133 regional cerebral blood flow, positron emission tomography (PET), brain electrical activity mapping (BEAM), and nuclear magnetic resonance scanning. This group directs the behavioral neurology service at St. Elizabeths Hospital.

- Section on Clinical Brain Studies—
  Joel E. Kleinman, M.D.
  Craig N. Karson, M.D.

A large human brain bank is the focus of postmortem studies that are evaluating neurochemical, immunologic, and virologic hypotheses of neuropsychiatric illness. Current projects include qualitative and quantitative neuroanatomy, immunocytochemistry, and studies of biogenic amine, peptide, and receptor neurochemistry. This section is also involved in the phenomenology of schizophrenia and related disorders including visual hallucinations, negative symptoms, eye-blinking, polydipsia, suicide, and aggression.

Laboratory of Preclinical Pharmacology—

- Section on Neuropeptides—
  Hsiu-Ying T. Yang, Ph.D.

Studies of neuropeptides operative in the regulation of pain threshold are carried out with target on the molecular mechanisms of tolerance and dependence to morphine. Enzymes involved in neuropeptide processing and inactivation are characterized and purified. cDNA probes for neuropeptide precursors are prepared.

National Institute of Neurological and Communicative Disorders and Stroke

Murray Goldstein, D.O., M.P.H.
Director
Irwin J. Kopin, M.D.
Director, Intramural Program
Ernst Freese, Ph.D.
Associate Director for Laboratories
Mark Hallett, M.D.
Clinical Director

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) provides broad opportunities for post-doctoral training in the basic and clinical neurosciences. Laboratories and clinics operated by the Institute are located principally on the main NIH campus in Bethesda, Maryland. Limited training opportunities also exist at NINCDS facilities in Frederick, Maryland, Woods Hole, Massachusetts, and on Guam. Most medical staff fellows participate in clinical neurosciences research in Institute laboratories and clinics, and have responsibility for the care of patients admitted for study. Some fellows primarily engage in basic laboratory investigations. All work is conducted under the preceptorship of a senior staff member and fellows are encouraged to avail themselves of an active program of teaching seminars, invited lectureships, and ward rounds.

Appointments in Clinical Research

Medical staff fellow positions for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) are available in medical and surgical neurology, experimental therapeutics, infectious diseases, neuroimmunology, neuroepidemiology, and developmental and metabolic neurology. Fellows are usually appointed for 2 years, with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on NINCDS wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NINCDS research emphases.

Candidates requiring further information about NINCDS clinical positions for medical staff fellows should write to Mark Hallett, M.D., Clinical Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 10, Room 5N226, National Institutes of Health, Bethesda, Maryland 20892.

Appointments in Laboratory Research

NINCDS medical staff fellow positions are available in neurochemistry, neurophysiology, neuropathology, neuro-otolaryngology, biophysics, molecular biology, biology, molecular genetics, and other areas of fundamental neurosciences investigation. Appointments are for 2 years, with the possibility of extended affiliation.

Areas of study are developed by each fellow in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which

the fellow is assigned. Independence and originality of approach are encouraged.

Medical staff fellows have the opportunity to work closely with a large and diverse group of senior investigators, to participate in on-site courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the NINCDS Medical Staff Fellowship Program, write to Irwin J. Kopin, M.D., Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 10, Room 5N214, National Institutes of Health, Bethesda, Maryland 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIDR programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 88.

Medical Staff Fellows in Neuroimaging

Intramural Research Program—
Irwin J. Kopin, M.D.

- Section on Neuroimaging—
  Giovanni Di Chiro, M.D.

Work in this section focuses on emission computed tomography (ECT) using positron emitting radionuclides (positron emission tomography-PET). The section is also very actively involved in nuclear magnetic resonance (NMR) imaging of the central nervous system. Emphasis is placed on correlative studies between PET and NMR imaging, as well as comparison with the more conventional neuroradiological techniques (CT, angiography).

Traditionally, this section has been involved in advanced radiographic and nuclear medicine equipment development. This approach will continue. Experimental animal studies will receive a new impetus with a soon-to-be installed 40 cm bore imager-spectroscopy device.

Clinical Branches

Developmental and Metabolic Neurology Branch—
Roscoe O. Brady, M.D.

- Section on Enzymology and Genetics—
  Roscoe O. Brady, M.D.

Principal research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic counseling related to inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with the development of enzyme purification procedures for replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and investigations of genetic mutations of cholesterol metabolism in experimental animals.

- Section on Neurochemical Methodology—
  Andrew E. Gal, Ph.D.

This section is involved in the preparation of widely useful substrates for the facile diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, and the synthesis of novel lipids and lipid analogs for metabolic studies in normal and pathologic tissues.

- Section on Myelin and Brain Development—
  Richard H. Quarles, Ph.D.

Research is primarily concerned with the composition and metabolism of myelin components in the developing nervous system and an examination of abnormalities of their structure and function in demyelinating conditions such as

multiple sclerosis and in peripheral neuropathies.

- Section on Molecular and Medical Genetics—
  John A. Barranger, M.D., Ph.D., Acting

The section conducts research on the biochemistry and molecular genetics of inherited disorders of metabolism. Work is focused on basic studies of lysosomal storage disorders. Projects include cDNA and genomic cloning of the genes for lysosmal enzymes, gene transfer, expression of genes in bacterial and mammalian cell genetic recombinants, gene assignment, DNA restriction fragment polymorphism, and the development of diagnostic methods in a variety of mutants.

- Section on Membrane Biochemistry—
  Peter H. Fishman, Ph.D.

Research is directed towards the biosynthesis, organization, and function of cell membranes including transmembrane signaling of receptor-mediated information, regulation of membrane enzymes, biogenesis of membrane components, and topologic organization of cell-surface receptors.

- Section on Clinical Investigations and Therapeutics—
  Roscoe O. Brady, M.D.

Basic research is conducted on the biochemistry of lysosomal glycoprotein enzymes. Structure, biosynthesis, subcellular localization, and properties of the enzymes responsible for their assembly into lysosomal membranes, *in vivo* activity, and turnover are examined. Applied research deals with the clinical diagnosis and study of the lysosomal storage disorders and clinical trials of novel therapies.

Experimental Therapeutics Branch—
Thomas N. Chase, M.D.

- Section on Pharmacology—
  Thomas N. Chase, M.D.

This section conducts an integrated program of preclinical and clinical studies directed towards the rational development of improved therapies for extrapyramidal and dementing disorders. Current investigations focus on the pharmacology of central transmitter systems; biochemical and cerebral imaging (positron emission tomography) approaches are used to related neurologic symptoms to dysfunction of specific classical or peptidergic systems. Pharmaceutical testing is carried out in animal models and in research patients.

- Biochemical Neuropharmacology Section—John Kebabian, Ph.D.

Research is conducted on relatively simple, peripheral tissues used as model systems of the interactions occurring in the central nervous system (CNS). The second messengers calcium and cyclic AMP and their effects upon protein phosphorylation are currently being studied.

- Section on Physiological Neuropharmacology—
  Judith Walters, Ph.D.

This section investigates neurophysiological aspects of neuronal function and drug action in the CNS, especially in the basal ganglia and substantia nigra. Current studies include investigation of the consequences of dopamine receptor stimulation, the modulatory interactions of dopamine with other neurotransmitters and dopamine-GABA-peptide interrelationships in the basal ganglia. Single unit recording and iontophoretic techniques are utilized in *in vivo* and *in vitro* slice preparations in conjunction with supportive biochemical procedures.

- Unit on Neuroendocrinology—
  Thomas O'Donohue, Ph.D.

The unit conducts preclinical investigations of regulatory processes in neuropeptide containing neurons which will eventually lead toward a better understanding of neurological disease and the development of new pharmacological therapeutic agents. The particular focus is on the mechanisms of regulation of gene expression of neuropeptide prohormones and neuropeptide processing enzymes. The methodologies used in the Lab include peptide and protein isolation and structural determination, gene cloning and isolation, gene transplant experiments, neuropeptide receptor identification, and histochemical techniques including immunosetic chemistry and *in situ* hybridization.

Infectious Diseases Branch—
John Sever, M.D., Ph.D.

- Section on Immunochemistry and Clinical Investigations—
  Sidney Houff, M.D.

The role of virus infections and their immunological responses are studied in relation to progressive multifocal leukoencephalopathy, polymyositis, Reye's syndrome, Echovirus encephalitis, multiple sclerosis, amyotrophic lateral sclerosis, CNS infections with Epstein-Barr virus infections and the neurological complications seen in AIDS patients. Persistent perinatal infections are also being investigated. Clinical research in these areas is combined with laboratory studies including experimental disease in monkeys and various other animals.

- Section on Neurovirology—
  Maneth Gravell, Ph.D.

This section is involved in research on viruses which cause persistent infections of the brain including PML, MS, and CNS-AIDS retroviruses as well as experimental models of persistent virus infections. Methods include tissue culture, cocultivation, new tests for cellular immunity, and antibody determinations.

- Section on Experimental Pathology—
  W. T. London, D.V.M.

Studies of perinatal and persistent central nervous system infections are conducted in monkeys and small laboratory animals. Papovaviruses, retroviruses, cytomegaloviruses, toxoplasmosis, and herpes viruses are being investigated. Methods for detection, treatment, and prevention are being developed. Persistent infections with polyomaviruses, progressive multifocal leukoencephalopathy, and glioblastomas are under investigation.

One medical staff fellow is appointed annually for 2 years. The individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as fellows for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Medical Neurology Branch—
Roger J. Porter, M.D.

- Section on Clinical Epilepsy—
  Roger J. Porter, M.D.

The section conducts intensive monitoring of patients with uncontrolled seizures by videotape recording and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents, and studies on the usefulness of new scanning procedures, such as positron emission tomography. Various clinical and electroencephalographic and magnetoencephalographic (MEG) aspects of seizure disorders are investigated, with emphasis on diagnosis and localization. Cerebral evoked response techniques are also applied for clinical and research studies. Consultative EEG, MEG, and cerebral evoked response examinations are provided to neurologic and psychiatric patients within the NIH. Basic investigations are focused on pathophysiologic and pharmacologic aspects, utilizing a kindling model of epilepsy. The appointment of medical staff fellows is for 2 years, and preference is given to applicants with experience in clinical neurology and electrophysiology.

- Section on Clinical Neuropharmacology—
  Ronald J. Polinsky, M.D.

The section investigates neurotransmitter function and metabolism in various neurological disorders. Assessment of the noradrenergic system in patients with chronic autonomic failure is performed by measuring the levels of catecholamines and their metabolites in blood, urine, and cerebrospinal fluid. Interrelationships among neurotransmitter, hormonal, and peptide systems are examined using several neuroendocrine and neuropharmacological approaches. There is also an experimental treatment program for patients with orthostatic hypotension.

A longitudinal study of clinical, biochemical, and neuropharmacological changes in familial Alzheimer disease is in progress. Collaborative investigations of genetic linkage and analysis in familial Alzheimer disease are being conducted. Other disorders currently studied in this section include narcolepsy, dystonia mus-

culorum deformans, Gilles de la Tourette syndrome, and Parkinson's disease. Initial appointment of medical staff fellows is for two years. Preference is given to candidates with training in clinical neurology.

- Section on Human Motor Control—Mark Hallett, M.D.

This section is concerned with the control of movement in man. Mechanisms of generation of normal movement, pathophysiology of disordered voluntary movement and pathophysiology of involuntary movements are the major interests. Investigations involve careful clinical evaluation, physiological investigation and radiological studies including positron emission tomography. Physiological investigations include electromyography, electroencephalography, and quantitative measures of mechanical movements of the relevant body parts. One unit is primarily interested in limb movement and another unit is primarily interested in speech movement. The appointment of Medical Staff Fellows is for two or more years.

Neuroepidemiology Branch—
Bruce S. Schoenberg, M.D.

This Branch conducts national and international studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The medical staff fellow receives training in the utilization of neuroepidemilogic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the Branch's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurofibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, epilepsy, racial differentials in the occurrence of neurologic disease, and international variation in the occurrence of neurologic diseases.

Neuroimmunology Branch—
Dale E. McFarlin, M.D.

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles which causes chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune diseases such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of unknown etiology, such as multiple sclerosis and Parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

Two medical staff fellows are appointed annually for 2 years. These individuals participate in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Surgical Neurology Branch—
Paul L. Kornblith, M.D.

This branch investigates and treats clinical problems of disordered neuronal and glial proliferation and differentiation. A major part of the program is devoted to the study of intracranial tumors including pituitary tumors. Problems of both central and peripheral neuronal and glial regeneration are also under study. Clinical research in these areas is combined with basic techniques of cell biology, tissue culture, biochemistry, immunology, pharmacology, and light and electronmicroscopic histology to provide for an in-depth exploration and, ultimately, new approaches to these problems.

Experimental neuropathology and neuroimmunology is emphasized in a program which includes clinical diagnostic neuropathology. Biochemistry, morphology, and immunochemistry of

neoplasms are studied as means of improving detection and treatment and as clonal models of their nonneoplastic counterparts in nervous and lymphoid tissues.

Studies are being carried out on cell-mediated immune mechanisms in human brain tumor patients, including delineation of the effectiveness of various forms of cell-mediated immunity to contribute to the destruction of brain tumors, examination of the ability of brain tumors to elicit cellular immune responses both *in vivo* and in model systems *in vitro,* and exploration of possible modes of altering brain tumor cells so as to increase their immunogenicity. This work is complemented by studies in animal models on basic mechanisms of cell-mediated immune lysis of tumor cells.

- Section on Clinical Neurosurgery—Edward H. Oldfield, M.D.

This section performs clinical research with emphasis on patients with primary tumors of the brain and spinal cord, pituitary tumors, vascular disorders of the central nervous system, and epilepsy. Investigation is designed to put findings from the basic laboratories into practice in the clinic. Current projects include (1) investigational treatment of malignant brain tumors with interstitial radioactive implants, intracarotid chemotherapy, phase I and II studies of new chemotherapeutic agents, and immunotherapy; (2) investigation and treatment of arteriovenous malformations of the spinal cord and brain; (3) *in vivo* and *in vitro* investigation of ACTH-, TSH-, and growth hormone-secreting pituitary tumors; and (4) the use of positron emission tomography in the investigation of drug delivery, blood-brain-barrier permeability, and the metabolism of brain tumors.

The medical staff fellow participates in the care of patients on the various protocols of the Clinical Neurosurgery Section as well as consultative care of patients with neurosurgical problems in all the NIH institutes. There will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, electron microscopy, and quantitative autoradiography. Experimental surgery and other studies in animal models as they relate to the clinical problems under study will also be performed. The fellow works in collaboration with senior scientists in specific laboratory areas as his or her experience and interest dictates.

Office of the Clinical Director— Mark Hallett, M.D.

This office has the responsibility for clinical neurological services to investigators within NINCDS and the other Institutes. Activities include clinical neurphysiological laboratory investigations, neurology consultations and neuropathology. Training opportunities emphasize development of clinical skills, but include application of these skills to clinically relevant research.

- EEG Laboratory—Susumu Sato, M.D.

The EEG laboratory offers both routine electroencephalography and evoked potential studies. Fellowship training satisfies requirements for taking the ABQEEG examination.

- Electromyography Laboratory—Mark Hallett, M.D.

The EMG laboratory offers routine electromyography and a number of special studies including single fiber electromyography and autonomic nervous system testing. The experience in fellowship satisfies requirements for taking the examination for active membership of the AAEE.

- Clinical Neurology and Neuropathology—Mark Hallett, M.D.

This division offers neurological consultation services including neurpathology. Research areas include neurological aspects of medical diseases. There has been particular emphasis on nerve and muscle disease in the research studies of Dr. Marinos Dalakas.

Basic Research Laboratories

Laboratory of Central Nervous System Studies—
D. Carleton Gajdusek, M.D.

This laboratory is engaged in two studies: (1) The medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning. High incidence and other unusual foci of chronic CNS diseases, asthma, parasitic and viral diseases, congenital metabolic defects, atypical patterns of puberty and aging, toxic and deficiency syndromes, and unusual behavior syndromes, where isolation or cultural stereotypy may contribute to epidemiologic solutions, are under study. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photography and sound recording. New methods of handling such data for research are developed. (2) The slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aging of the brain, Alzheimer's, Pick's, Parkinson's, and Huntington's diseases, multiple sclerosis, amyotrophic lateral sclerosis, chronic epilepsies, and other diseases are intensively studied in microbiological, immunologic, genetic, and biochemical laboratories and clinics and in foci of high incidence throughout the world.

Within this framework intensive investigation of epidemic hemorrhagic fever/hemorrhagic fever with renal syndrome is being conducted on a worldwide basis on the isolation and characterization of the virus, its molecular nature and immunogenetics, its seroepidemiology, and the documentation of mild forms of the disease in man.

Laboratory of Molecular Genetics—
Robert A. Lazzarini, Ph.D.

This laboratory investigates the component molecular events that participate in the replication and expression of the genetic materials of mammalian cells and their viruses. Genetic, biochemical, and recombinant DNA techniques are employed in the study of the replication and transcription of genes that ultimately lead to their expression as protein. These studies are directed toward a full understanding of the delicate interplay between the complementing genetic elements in normal cells, chimeric cells, and cells persistently infected with viruses.

- Molecular Virology Section—
  Robert A. Lazzarini, Ph.D.

  This section studies aspects of virus-host interactions at the molecular level. These include viral penetration of host cells, viral replication, and the assembly of progeny particles. Particular attention is focused on the involvement of host factors in the replication of the viral genome and the relationship of these to viral host range, persistency, latency, and cytopathology.

- Recombinant Genetics Section—
  Robert A. Lazzarini, Ph.D.

  Studies are under way of eukaryotic gene expression and genetic complementation in cultured mammalian cells. These studies employ both recombinant DNA and classical biochemical techniques to probe the control of gene transcription, the processing of primary transcripts, and eventual expression of these RNA's as proteins.

- Neural and Molecular Ultrastructure Section—
  Monique Dubois-Dalcq, M.D.

  Studies are under way on: (1) growth

factors and purification methods of rodent and human nerve cells, and (2) how nerve cells are affected by neurotropic viruses. More specifically, virus tropism and assembly is studied in nerve cells as well as susceptible cells. Methods employed consist of immunolabeling for light and electron microscopy as well as microinjection of monoclonal antibodies to viral proteins into living cells. (3) The emergence and assembly of myelin proteins during nervous system development using immunocytochemical methods are examined. Similar methods are used to study the alternations in myelin proteins in diseased nerves.

Laboratory of Neural Control—
Robert E. Burke, M.D.

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the CNS control of spinal cord motorneurons and in turn the control exerted by these cells on the muscle fibers innervated by them, 2) the organization of information-processing systems in the spinal cord, and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—
Janet V. Passonneau, Ph.D.

Research is conducted on molecular events that underlie the normal functioning of the nervous system and derangements that occur in neurologic diseases.

- Section on Cellular Neurochemistry—
  Janet V. Passonneau, Ph.D.

Section is involved in studies on metabolism in neural tissues. Emphasis is placed on the microanalytical techniques used to measure metabolites in discrete regions of the brain or in single cells. In the retina the metabolic response of retinal layers to light and dark adaptation is studied, and Dr. Ralph Nelson investigates the light responses of individual cells by intracellular electrophysiological techniques. Other projects include the regional alterations of energy metabolites in ischemic brain, the role of guanine nucleotides in brain function, glycogen metabolism and protein synthesis.

- Section on Enzyme Chemistry—
  Wayne Albers, Ph.D.

This enzymatic mechanism of active Na^+ and K^+ transport is investigated. Other current projects involve g-aminobutyric acid metabolism brain mitochondria, and membrane receptors.

- Section on Neuronal Development and Regeneration—
  Andrew Zalewski, M.D.

This section is attempting to elucidate the factors involved in nerve fiber regeneration, trophic nerve function, and selectivity and plasticity in the formation of neural connections. A variety of neurohistologic, histochemical transplantation, and immunologic techniques are being used in these studies.

Laboratory of Neuro-Otolaryngology—
Jorgen Fex, M.D., Ph.D.

Inner ear neuronal mechanisms are being studied in mammals. The long-range purpose of the project is to study the biochemistry, morphology, pharmacology, and physiology of inner ear neurons and cells and their interactions and to describe the mechanisms of these interactions. A second project concerns the synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A multidisciplinary approach is being used for this project. A major, long-term program of this laboratory is to solve problems concerning hereditary deafness in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

Laboratory of Cerebral Vascular Neuropathology—
Igor Klatzo, M.D.

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system.

- Section on Cerebrovascular Pathology—Igor Klatzo, M.D.

Research is conducted on various aspects of pathophysiology of cerebral ischemia and brain edema. Elucidation of the pathomechanisms involved is attempted by evaluation and correlation of various parameters, such as changes in blood flow, electrical impedance, water content, electrolytes, glucose metabolism, behavior of the blood-brain barrier, and morphological alterations in various models of ischemia and traumatic brain injury.

- Section on Neurocytobiology—Maria Spatz, M.D.

This section investigates the normal and pathological properties of cerebral endothelium which is the main substrate of the blood-brain barrier. The investigations include observations on transport mechanisms in endothelial cells, on their receptors, and on the effect of various substances in modifying barrier phenomena and the course of edema and ischemia.

Laboratory of Experimental Neuropathology—
Henry deF. Webster, M.D.

This laboratory studies cellular mechanisms of myelin formation, maintenance and breakdown with special emphasis on roles viruses may have in multiple sclerosis and other demyelinating diseases. Virological, immunocytochemical, immunological, biochemical and biophysical techniques are being used in current projects.

Laboratory of Neurobiology—
Thomas S. Reese, M.D.

Conducts structural research on the organization of the nervous system. Specific cell biological problems are synaptic transmission, glial function, axoplasmic transport, organization of glial and neural membranes, and the intracellular sequestration of ions. The principal organizational problems investigated are the blood-brain barrier, and neural development and regeneration. Structural tools used are electron-microscopy, X-ray spectroscopy, immunocytochemistry, cryotechniques, and computer processed imaging.

- Section on Functional Neuroanatomy—Thomas S. Reese, M.D.

This section is primarily concerned with studies on synaptic structure and function, redistribution of elements during neuronal activity and secretion, instrinsic membrane proteins and lipids, and neuronal cytoskeleton. Using modern electron optical and low temperature techniques, the structure of neural cells and membranes is investigated in close to molecular level of resolution.

- Section on Structural Plasticity—Milton W. Brightman, Ph.D.

The section is engaged in studies to delineate the conditions necessary for the placement, survival, regeneration, and function of transplanted neurons—both peripheral and central, to characterize further the tropism between central and peripheral neurons and to analyze the structural changes in astrocytic cell membranes during degeneration and regeneration.

Laboratory of Neurophysiology—
Jeffery L. Baker, M.D.

All of the laboratory's projects involve multi-disciplinary analysis of the physiological properties of vertebrate central neurons studied *in vitro*. The techniques utilized encompass many of those current in cellular neurobiology, including electrophysiology, immunohistochemistry, electronmicroscopy, flow cytometry and dissociated cell culture. A principal line of investigation is focused on the physiological properties of neurons cultured from different parts of the mammalian

CNS, since monolayer cultures allow immediate accessibility to quantitative analysis of neuronal function at the cellular level. Using such a strategy, members of the laboratory are studying which properties are resident in different types of nerve cells, how these properties evolve during embryonic development, and what roles they play in intercellular communication. These studies are thus aimed at providing insight primarily into the question of what types of phenotypic properties are expressed by different CNS cells and secondarily into the related problem of how these properties differentiate the functions of one cell type from another. One long-term goal of the laboratory is a better understanding of the relationship between the activity of ion channels in neuronal membranes and the synthesis and secretion of specific transmitter substances.

Another area of considerable activity in the laboratory involves pharmacological experiments on the cellular mechanisms of actions of clinically important drugs like benzodiazepines, barbiturates, and convulsants using electrophysiological recording techniques (voltage-clamp and patch-clamp).

Laboratory of Molecular Biology—
Ernst Freese, Ph.D.

Developmental effects of mutations and drugs are examined. They are correlated to hereditary diseases and teratogenic effects.

- Section on Developmental Biology—
  Ernst Freese, Ph.D.

  The control of cell differentiation in microorganisms and brain cells is investigated by biochemical, immunochemical, and genetic engineering methods. Changes in gene expression are analyzed during development, during neuron-astrocyte interactions, in hepatic encephalopathy, and in human gliomas.
- Section on Molecular Neurobiology—
  Richard Henneberry, Ph.D.

  Studies are designed to further our understanding of the mechanisms by which individual cells respond to external signals. Cell surface receptors for hormones and neurotransmitters, in particular those whose function involve modulation of cAMP levels are investigated using the methods of biochemistry and biology.

Laboratory of Biophysics—
William J. Adelman, Jr., Ph.D.

Studies are under way on molecular, single-channel, and cellular mechanisms of excitation and ion conductance; membrane potentials and currents; generation of nerve and muscle impulses; synaptic activity; structural and chemical basis for axoplasmic and neuroplasmic transport; the biophysical basis for the functioning of simple nervous systems; the cellular basis for integrative neural functions such as behavior and learning; biophysical neuropharmacology and molecular basis for rhythmic and spontaneous activity in neurones and skeletal and cardiac muscle. Such studies utilize physical and chemical techniques, digital computers, electron and light microscopy, and a variety of applied mathematical methods.

The Clinical Center

John L. Decker, M.D.
Director

Department of Transfusion Medicine—
Harvey G. Klein, M.D.

Staff Fellowship

The Department of Transfusion Medicine accepts applications for an American Medical Association accredited fellowship program in blood banking and immunohematology. The fellowship assignment is usually for 2 years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is required.

The program offers training in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. The fellow receives broad experience in all aspects of transfusion medicine, including clinical and laboratory immunohematology, apheresis techniques, tissue typing, donor recruitment, and blood component preparation and therapy. The fellow participates actively in the service and teaching functions of the department.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various institutes. Current programs include investigations into the various agents responsible for posttransfusion hepatitis, the effects of biologic incompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and innovative uses of automated apheresis techniques.

Prospective applicants desiring more information should write to Richard J. Davey, M.D., Program Director, Department of Transfusion Medicine, Building 10A, Room 1E33, National Institutes of Health, Bethesda, Maryland 20892.

Clinical Pathology Department—

Ronald Elin, M.D., Ph.D.

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the institutes. The department is organized into three services: clinical chemistry, hematology, and microbiology. In addition, there is a close working relationship with the Information Systems Management Department. The Clinical Chemistry, Hematology, and Microbiology Services and the Information Systems Management Department, offer medical staff fellow positions, but not necessarily on a yearly basis.

• Clinical Chemistry—

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of five individuals with M.D. and/or Ph.D. degrees. Approximately 200,000 tests are performed per month by a technical staff of 42 medical technologists, chemists, technicians, and medical aides. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of radioimmunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference range, instrument evaluation, and automated assay.

A medical staff fellow entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, radioimmunoassay, urinalysis, special chemistry, and SMAC. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The fellow would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the fellow would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the fellow would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Medical Staff Fellow Program should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 2C-407, National Institutes of Health, Bethesda, Maryland 20892.

• Hematology—

The Hematology Service provides clinical and research experience in hematology. We have an active clinical and consultative service. The Hematology Service also has a research program directed at clinical and basic problems in Hematology. The service is responsible for the operation of the routine clinical hematology, coagulation, and special hematology laboratories. Basic research interests include blood coagulation, protein purification and characterization, interactions of coagulation proteins, characterization of binding proteins to platelets. Other research endeavors include the use of immunologic and biochemical markers for hematopathologic diagnoses including flow cytometry and the development and testing of new procedures of analytic systems in the hematology laboratories.

The Hematology Service recruits medical staff fellows for a minimum of 2 years. Some fellows will spend at least 6 months doing primarily clinical work with patients in the Clinical Center. During this time, the fellow will also have the opportunity to develop a specific interest in investigative studies. Fellows will be encouraged to choose a problem for investigation which can be pursued with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Medical staff fellows whose primary interest is basic or laboratory research are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, these fellows will devote most of their time to laboratory research. The candidate who is chosen will be given an opportunity to choose an area of investigation, and a senior staff member will serve as his or her preceptor.

Any candidate interested in either program should write to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 2C390, National Institutes of Health, Bethesda, Maryland 20892.

• Microbiology—

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training program is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, evaluation of automated reading devices for identifying bacteria, and the evaluation of new methodologies for antibiotic sensitivity testing. A variety of clinicopathologic studies is also undertaken or could be initiated under senior staff supervision.

Persons interested in a medical staff fellowship position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 2C-385, National Institutes of Health, Bethesda, Maryland 20892.

• Laboratory Computer—

The Information Systems Management Department provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes pathologists, programmers, and computer operators. In addition to its own minicomputer systems, the service makes extensive use of the NIH IBM 370 and DEC PDP-10 time-sharing computers. Investigators in the service utilize exten-

sive machine-readable files of clinical and laboratory information pertaining to NIH patients.

A medical staff fellow works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Fellows are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department. Appointments are for a period of 2 years and are not made yearly.

Interested candidates should write to Thomas L. Lewis, M.D., Associate Director for Information Systems Management, Clinical Center, Building 10, Room 2C-137, National Institutes of Health, Bethesda, Maryland 20892.

Critical Care Medicine Department—
Joseph E. Parrillo, M.D.

The Critical Care Medicine Department is offering 2- to 3-year fellowships in critical care medicine. To be eligible, a physician must have completed 3 years of residency in internal medicine, anesthesiology, or general surgery. The fellowship consists of a first year of clinical training in critical care medicine in the intensive care units at the National Institutes of Health and in the medical-surgical intensive care unit at a major regional trauma center. The clinical training provides broad experience in the care of critically ill patients and in a wide variety of procedures necessary to critical care. The second year (and an optional third year for selected fellows) consists of an individually designed program in clinical investigation or basic laboratory research related to critical illnesses. The NIH Fellowship Program is designed to satisfy all the subspecialty Board requirements for critical care medicine. Critical Care Medicine Boards are planned for the first time in 1986.

The fellowship program is designed to provide excellent clinical training in the care of extraordinarily sick patients with multisystem organ dysfunction. Critical care physicians in the NIH ICU have primary responsibility for care of the patient. The critical care physicians work closely with referring physicians and call on multiple consultative services necessary to give full intensive care to these patients. The Critical Care Medicine Department consists of a senior staff that has subspecialty training in cardiology, pulmonary diseases, anesthesiology, infectious diseases, and critical care medicine. The staff performs most of the invasive procedures (Swan Ganz catheterization, cardiac catheterization, bronchoscopy, etc.) themselves in a specially constructed procedure/catheterization laboratory in the ICU. The ICU also has capability for computer processing and analysis, noninvasive (echocardiography, nuclear scanning) cardiac diagnostic studies, and pulmonary function studies.

The fellowship research training is designed to produce independent clinical investigators in the field of critical care medicine. The educational program includes weekly conferences on clinical critical care medicine and seminars regarding ongoing research programs in the department. Each fellow will have a senior staff member guiding the investigations. Ongoing research in the department includes the following: studies of hemodynamics and cardiovascular function in different forms of shock; the immunopathogenesis of septic shock; capillary leak syndromes; pulmonary functional abnormalities in shock lung; studies of immune cellular function in shock lung, asthma, and other forms of severe pulmonary disease; critical care of the immunocompromised host; and studies of immune cellular function and therapy of the acquired immune deficiency syndrome (AIDS).

Applications must be completed by November 14, nineteen months prior to the anticipated start of the fellowship.

For further information on the program, please contact Joseph E. Parrillo, M.D., Chief, Critical Care Medicine Department, Building 10, Room 10D48, National Institutes of Health, Bethesda, Maryland 20892.

Nuclear Medicine Department—
Steven M. Larson, M.D.

One medical staff fellow is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in nuclear medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved internal medicine, radiology, or clinical pathology is recommended to meet the requirements for certification by the American Board of Nuclear Medicine.

Residency Training

The American Medical Association has approved the department for a 2-year residency training program in nuclear medicine. Qualifications for trainees include at least 2 years of prior training in radiology, pathology, or internal medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital or the Maryland University Hospital.

The department consists of three sections: The Diagnostic/Therapeutics Section, The Applied Physics Section, and the Radiopharmaceutical Chemistry Section.

The Diagnostic/Therapeutic Section provides clinical and investigative service to the physicians of the various institutes working within the Clinical Center. Rectilinear scanners and gamma cameras are the basic imaging devices. Within this section, the Positron Emission Tomography group provides positron imaging capability for the study of a broad range of conditions. Currently the emphasis has been on brain glucose metabolism in a variety of disease states and in normal conditions. This section is staffed by physicians and technicians who have the responsibility for clinical research imaging.

The radiopharmaceutical chemistry section has responsibility for the cyclotron production of positron-chemistry radiopharmaceuticals and also includes a radiopharmacy group, with broad responsibility for assuring the radiopharmaceutical purity and quality of all radioisotopes used for tumor use, throughout NIH.

The Applied Physics Section works toward the development of new data processing techniques. Computers for processing nuclear medicine data are located within the section. Department professionals are encouraged to interact with members of the various institutes to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases. The department also provides consultations and support for the use of radionuclides in diagnosis and research.

Division of Computer Research and Technology

Arnold W. Pratt, M.D.
Director

The Laboratory of Applied Studies, DCRT, offers 2-to 3-year medical staff fellowship positions to physicians with additional training in physical science or engineering (including mathematics through differential equations), 2 years experience in computer programming, and at least 1 year of residency (internship).

Laboratory of Applied Studies—
James J. Bailey, M.D.

This laboratory engages in independent and collaborative research on innovative applications of mathematics, computer science, and engineering to problems of

clinical medicine and basic biology. The senior staff includes mathematicians, physicians, electronics engineers, and computer systems analysts; and facilities include access to micro-, mini-, and main frame computer systems (i.e. IBM-XT, DEC 11/23, Masscomp MC500, IBM 370, and DEC-10).

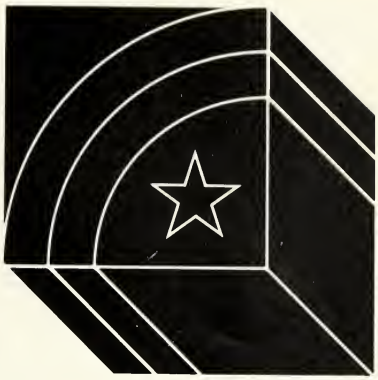
The fellow will collaborate with clinicians or bench lab scientists in one or more of such current projects as: (1) Biological signal analysis, e.g., monitoring and interpretation of evoked potentials for assessment of central nervous system function in the critically ill, investigating the dynamics of gas exchange in exercising subjects, evaluating electrophysiologic responses to cardiotoxic drugs and infective myocarditis. (2) Analysis of multimodality images to correlate structure and function, e.g., PET scans, single photon tomography, 3D visualization, and pattern recognition. (3) Development of mathematical modeling tools and database analysis algorithms, e.g., spatial and temporal representation of laboratory acquired neuronal data, body surface potential maps, receptor binding and reaction-diffusion kinetics.

The fellow will be guided by the senior staff, especially in such areas as: modeling of physiologic processes, mathematical methodology, signal analysis, image processing, and computer automation.

Interested candidates should contact: James J. Bailey, M.D., DCRT, Building 12A, Room 2041, National Institutes of Health, Bethesda, Maryland 20892.

Part Four

Academic Programs Available to Medical Staff Fellows



Among the academic programs open to an NIH medical staff fellow are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc. (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 40 to 50 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the FAES Graduate School, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The FAES is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters, fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. The FAES and the Clinical Center sponsor board review courses in medicine and pediatrics. Subspecialty courses are offered for board review in endocrinology, hematology, and oncology. Further inquiries regarding the Graduate School and requests for its current catalog should be directed to: Registrar, Foundation for Advanced Education in the Sciences, Inc., Graduate School, National Institutes of Health, Bethesda, Maryland 20892.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is conducted by one of the institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff and serve to keep individual investigators abreast of current emphasis in all clinical research.

Topics Presented in the 1985-86 Series Were:

February 12, 1985	Neal Cutler, M.D.	Alzheimer's Disease: New Insights
March 12, 1985	Ronald Crystal, M.D.	Alpha-1 Antitrypsin Deficiency
March 26, 1985	Joseph Parrillo, M.D.	Septic Shock
April 9, 1985	George Merriam, M.D.	Diagnostic and Therapeutic Application of Growth-Releasing Factors
May 14, 1985	Warren Strober, M.D.	Crohn's Disease
November 26, 1985	Mitchell Max, M.D.	New Approaches to the Study of Pain and Analgesia
January 22, 1986	George Chrousos, M.D.	The Clinical Applications of a Glucocorticoid & Progesterone Antagonist
February 26, 1986	Vincent DeVita, M.D.	Developmental Therapeutics in Cancer and the Acquired Immunodeficiency Syndrome
March 26, 1986	Thomas Waldmann, M.D.	The Interleukin-2 Receptor: Clinical and Molecular Correlations in Normals and Patients with Cancer
April 23, 1986	Thomas Uhde, M.D.	Phenomenology & Neurobiology and Panic Disorder
May 21, 1986	James Balow, M.D.	Lupus Nehritis
June 11, 1986	Anthony Fauci, M.D.	Use of Immunomodulators in Clinical Medicine

Several formal lectures are presented annually. **The National Institutes of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the institutes. Dr. S. Dillon Ripley of the Smithsonian Institution gave the most recent NIH lecture in December 1984 on "Twenty Years A' Growing."

The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Louis Miller of the National Institute of Allergy and Infectious Diseases presented the 1985 Dyer lecture on "Malaria: Cell Surface Proteins as Receptors and Immunogenes." Among other distinguished speakers have been Nobel laureates Dr. Howard M. Temin, who spoke on "The Replication and Possible Origin of RNA Viruses with a DNA Polymerase," and Dr. D. Carleton Gajdusek, who discussed his work on kuru.

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1985	**Edward Korn, Ph.D.**	Biochemical Regulation of Actomyosin-Dependent Cell Motility
1984	George Khoury, M.D.	Enhancers: Regulatory Elements in Eukaryotic Gene Expression
1982	William E. Paul, M.D.	Living with Lymphocytes, or B Lymphocytes and How They Grow
1981	Louis Sokoloff, M.D.	Metabolic Mapping of Local Functional Activity in the Central Nervous System
1980	Thomas Waldmann, M.D.	The Control of the Immune Response Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation
1979	Martha Vaughan, M.D.	Regulation of Cyclic Nucleotide Metabolism
1978	Jesse Roth, M.D.	Receptor Disorders in Man
1977	Philip Leder. M.D.	A Close and Surprising Look at the Mammalian Genome
1977	Maxine F. Singer, Ph.D.	Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA
1975	Karl A. Piez, Ph.D.	Collagen: Its Chemistry, Structure and Function

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional educational opportunities. Some medical staff fellows augment their experience at NIH with studies at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open-stack, self-service library with a collection of some 272,000 volumes of medical and scientific books and journals. Some 2,000 new books and 3,700 journal subscriptions are received annually. An integral part of the research needs of the NIH staff, the NIH library's major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation, and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs, and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 3 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the library's computerized data base of journal references (MEDLINE) is available both at NLM and at the NIH library.

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